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The British Journal of Surgery

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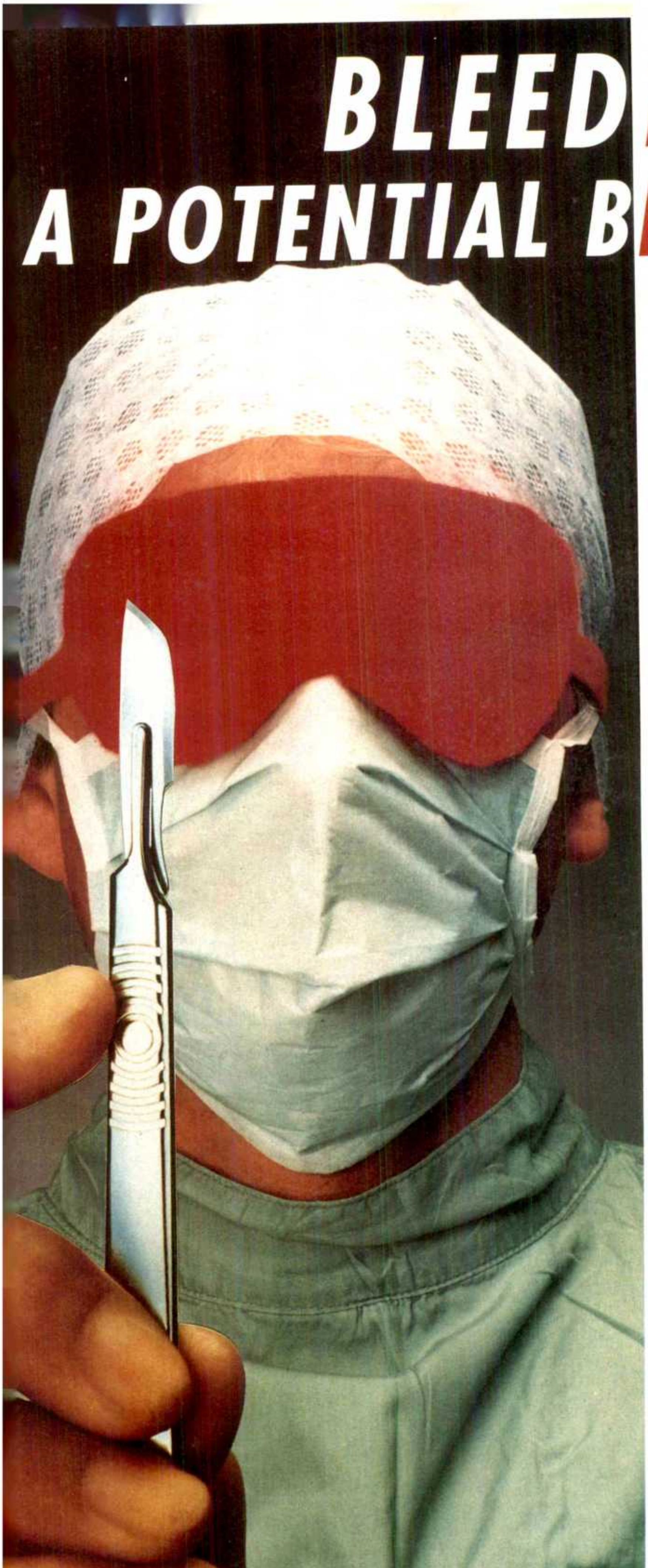

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- HIGH FLUID RETENTION

which combine to provide major benefits including:

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ALGISTAT Active Haemostatic Surgical Absorbent. **Presentation** Soft white sterile patterned absorbent felt of calcium alginate fib incorporating an X-ray detectable strip. **Uses** As an adjuvant in the control of haemorrhage during surgery and to absorb fluids from intra-operative bleeding. ALGISTAT must be removed before the incision is closed at the end of surgery. **Dosage and Administration** There is no difference in the treatment of adults, children or the elderly. ALGISTAT is applied to areas of capillary oozing and venous bleeding. **Contraindications, warnings, etc** Remove ALGISTAT when bleeding has stopped, or when maximum absorbency has been reached. ALGISTAT must be removed at the end of surgery, be skin closure. Animal studies have shown that if calcium alginate left in-situ on wound closure, a local intense inflammatory response is observed and adhesions will be produced. Although rar hypersensitivity reactions to the product may occur. ALGISTAT not intended to replace normal surgical practices for controlli bleeding. The physical characteristics of ALGISTAT differ from t of conventional cotton gauze swabs. It is unsuitable for applicatio where the latter are employed for their physical characteristics. These include the application of fluids to surfaces, as tempor covers, e.g. over the ends of resected bowel, for the application traction to tissues, or in "blunt" dissection. **Use in pregnancy** The effect of alginates during pregnancy and lactation has not be studied, but no hazard in their use is anticipated. **Pharmaceuti precautions** Store in a cool, dry place. Not to be resterilis **Legal Category** P **Package Quantities** 10cm x 10cm, sach containing 3 absorbents, carton of 10 sachets £75. 10cm x 20cm, sachet containing 2 absorbents, carton of 10 sachets £90. Product Licence No: PL 6079/0009

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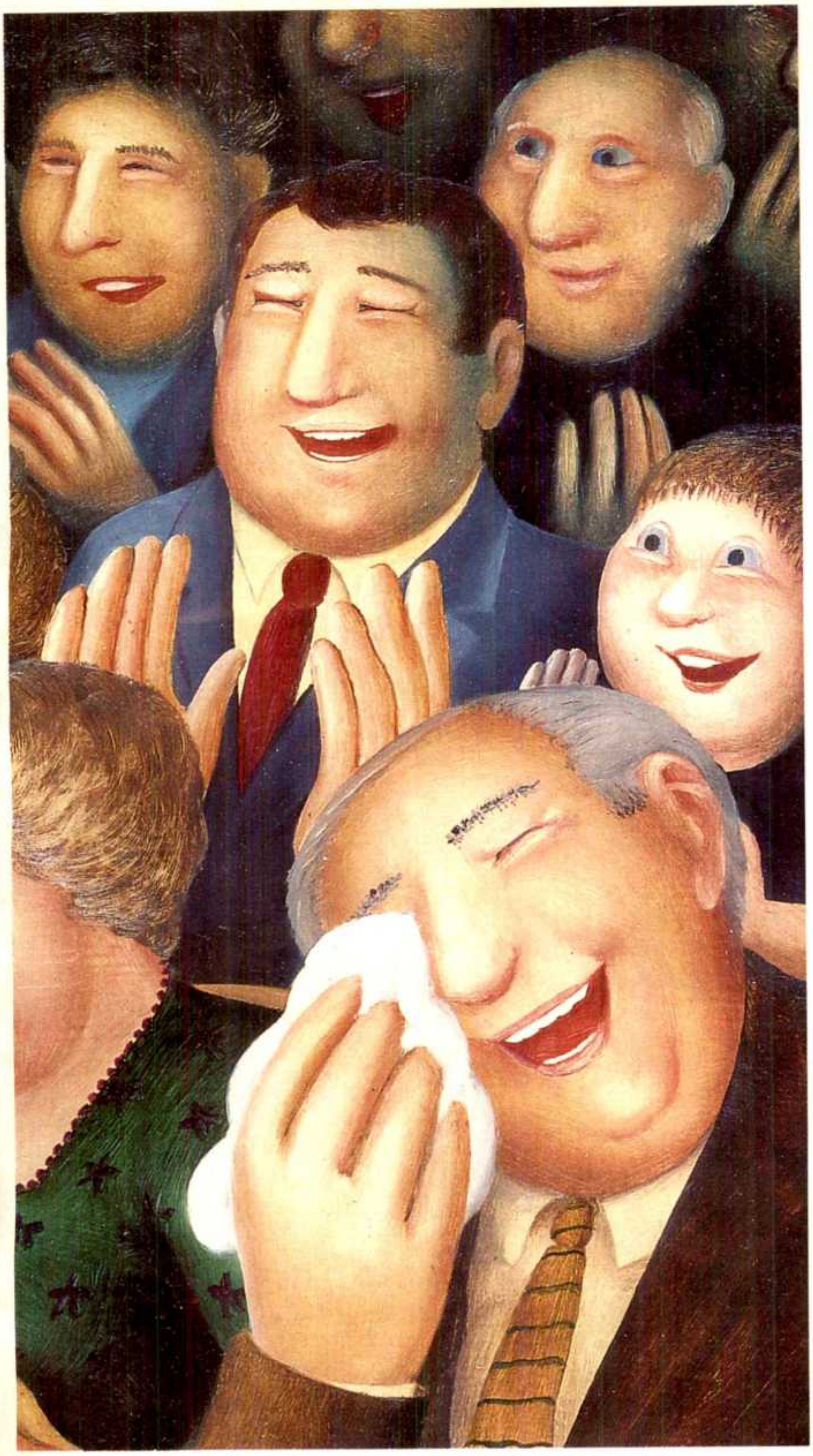
"They say laughter is the best medicine . . . when I was first told what I'd got I thought I'd never want to laugh again."

In a recent study[1] comparing the quality of life of prostate cancer patients receiving 'Zoladex' compared with those being treated with orchidectomy, it was found that men receiving 'Zoladex' gained a number of improvements in several important aspects of their lives.

Profile of Mood States (POMS) was used to assess such feelings as tension, depression, fatigue and vigour, while Functional Living Index: Cancer (FLIC) was used to measure physical ability, sociability, emotional state and family interaction.

The results of this study suggest that only the patient group treated with 'Zoladex' maintained a higher level of quality of life compared to their pre-treatment values.

Zoladex
goserelin

Treats the disease, enhances quality of life![1]

PRESCRIBING NOTES. Consult data sheet before prescribing. USE: Prostate cancer suitable for hormonal manipulation. **PRESENTATION:** A sterile depot containing goserelin 3.6mg. **DOSAGE AND ADMINISTRATION:** One depot injected subcutaneously into the anterior abdominal wall every 28 days. **CONTRAINDICATIONS:** Hypersensitivity to LHRH analogues. **PRECAUTIONS:** Patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. An increase in benign pituitary tumours has been observed in male rats following long-term repeated dosing. This finding is similar to that previously noted in this species following surgical castration (relevance to man not established). In mice, long-term repeated dosing with multiples of the human dose produced pancreatic islet cell hyperplasia and a benign proliferative condition of the pyloric region, also reported as a spontaneous lesion in this species (clinical relevance unknown). **SIDE EFFECTS:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. Isolated cases of ureteric obstruction and spinal cord compression. **LEGAL CATEGORY:** POM. **PRODUCT LICENCE NUMBER:** (29/0198). **BASIC NHS COST:** £125.40 per depot. **'Zoladex' is a trademark.**

Further information is available from: ZENECA Pharma, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ. ZENECA Pharma is part of the ICI Group.

Reference: 1. Cassileth BR, Soloway MS, Vogelzang NJ, *et al.* Quality of Life Research 1992; **1:** 323-330.

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The Surgical Research Society

What every surgeon should know..

Thromboembolic complications still remain a common problem after surgery.[1] A number of studies have shown that the risk of thromboembolic complications after surgery can be significantly reduced by thromboprophylaxis.[2]

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References: **1.** Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. **2.** Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmona embolism and venous thrombosis by perioperative administration of subcutaneous heparin. New Engl J Med 1988; 318:1162-1173. **3.** Bergqvist D, Mätzsch T, Burmark U S et al. Low molecular weight hepa given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888-891. **4.** Eriksson B I, Kälebo P, Anthmyr B O et al. Prevention of Deep-Ve Thrombosis and Pulmonary Embolism After Total Hip Replacement. J Bone Joint Surg 1991;73A (4):484-493.

Further information is available from: **Kabi Pharmacia Cardiovascular, S-112 87 Stockholm, Sweden**

Coated VICRYL* (Polyglactin 910) Braided Synthetic Absorbable Suture, Sterile

PRESENTATION VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide in the ratio 90/10. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)_m(C_3H_4O_2)_n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided VICRYL suture material with a mixture composed of a copolymer of lactide and glycolide in the ratio of 65/35 and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

Coated VICRYL (Polyglactin 910) is available in non-needled lengths or attached to stainless steel needles of varying types and sizes, and is sterilised by ethylene oxide gas.

These sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the *in vivo* behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

The general mechanism by which *in vivo* degradation of VICRYL (Polyglactin 910) occurs is hydrolysis.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at 14 days post-implantation approximately 65% of the original tensile strength remains. At 21 days approximately 40% of the original strength is retained for gauge sizes Metric 0.7 (6/0) and larger, and approximately 30% of the original strength is retained for gauge sizes Metric 0.5 (7/0) and smaller. All of the original tensile strength is lost between 28 and 35 days post implantation.

Intramuscular implantation studies in rats show that the absorption of these sutures occurs thereafter and is complete between the 56th and 70th day.

USES Coated VICRYL Synthetic Absorbable Sutures are intended for use where an absorbable suture or ligature is indicated.

DOSAGE AND ADMINISTRATION By implantation.

CONTRA-INDICATIONS, WARNINGS, ETC These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) in neural tissue and in cardio-vascular tissue have not been established.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when Coated VICRYL (Polyglactin 910) Sutures are used in ophthalmic procedures.

Under certain circumstances, notably orthopaedic procedures, immobilisation by external support may be employed at the discretion of the surgeon.

Coated VICRYL (Polyglactin 910) Sutures, which are treated to enhance handling characteristics, require the standard surgical technique of flat and square ties with additional throws if indicated by surgical circumstances and the experience of the operator.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

PHARMACEUTICAL PRECAUTIONS Recommended storage conditions: Below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack. Do not re-sterilise the contents of the pack. Unused product from opened packs should be discarded. As with all sutures, care should be taken to avoid damage when handling. Avoid the crushing or crimping application of surgical instruments, such as needle holders and forceps to the strand, except when grasping the free end of the suture during an instrument tie.

LEGAL CATEGORY Not applicable.

PACKAGE QUANTITIES Coated VICRYL (Polyglactin 910) is available in various lengths in gauge sizes Metric 0.4 to 5.0 (8/0 to 2) and 3 metre lengths on LIGAPAK* reels Metric 2.0 to 4.0 (3/0 to 1). All products are sealed in aluminium foil packs and peel-apart overwrap pouches. The sales unit is a film-wrapped box containing 10, 12 or 24 packs.

FURTHER INFORMATION No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

PRODUCT LICENCE NUMBER 0508/0009.

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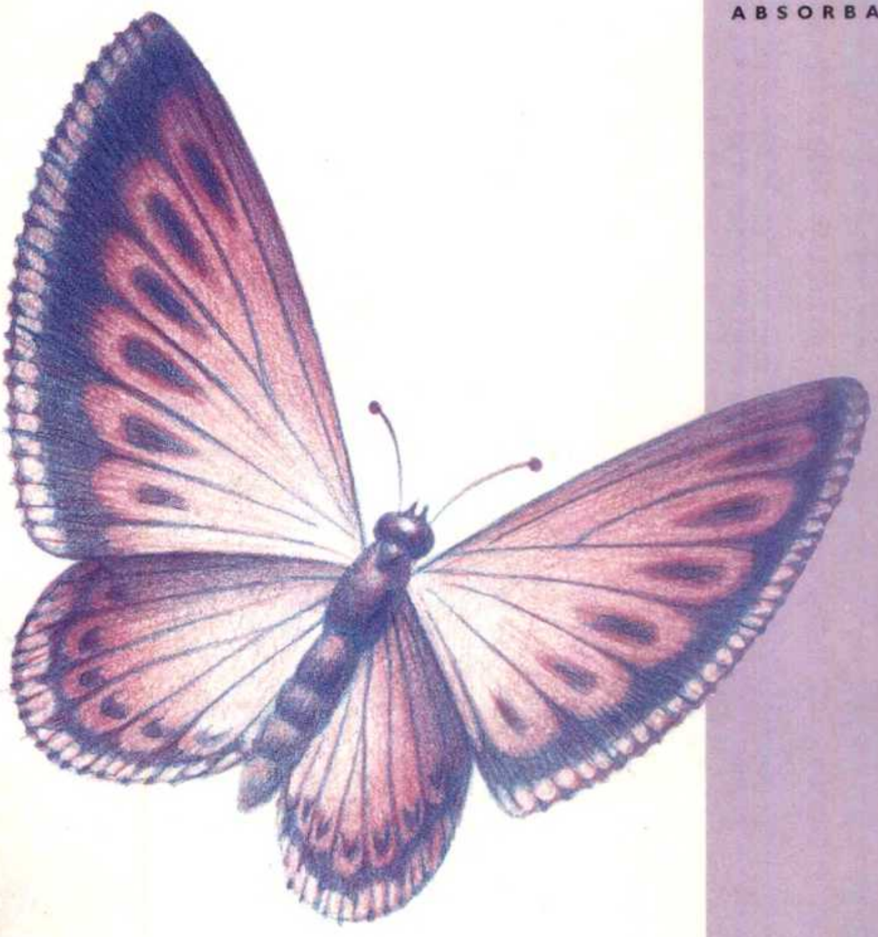

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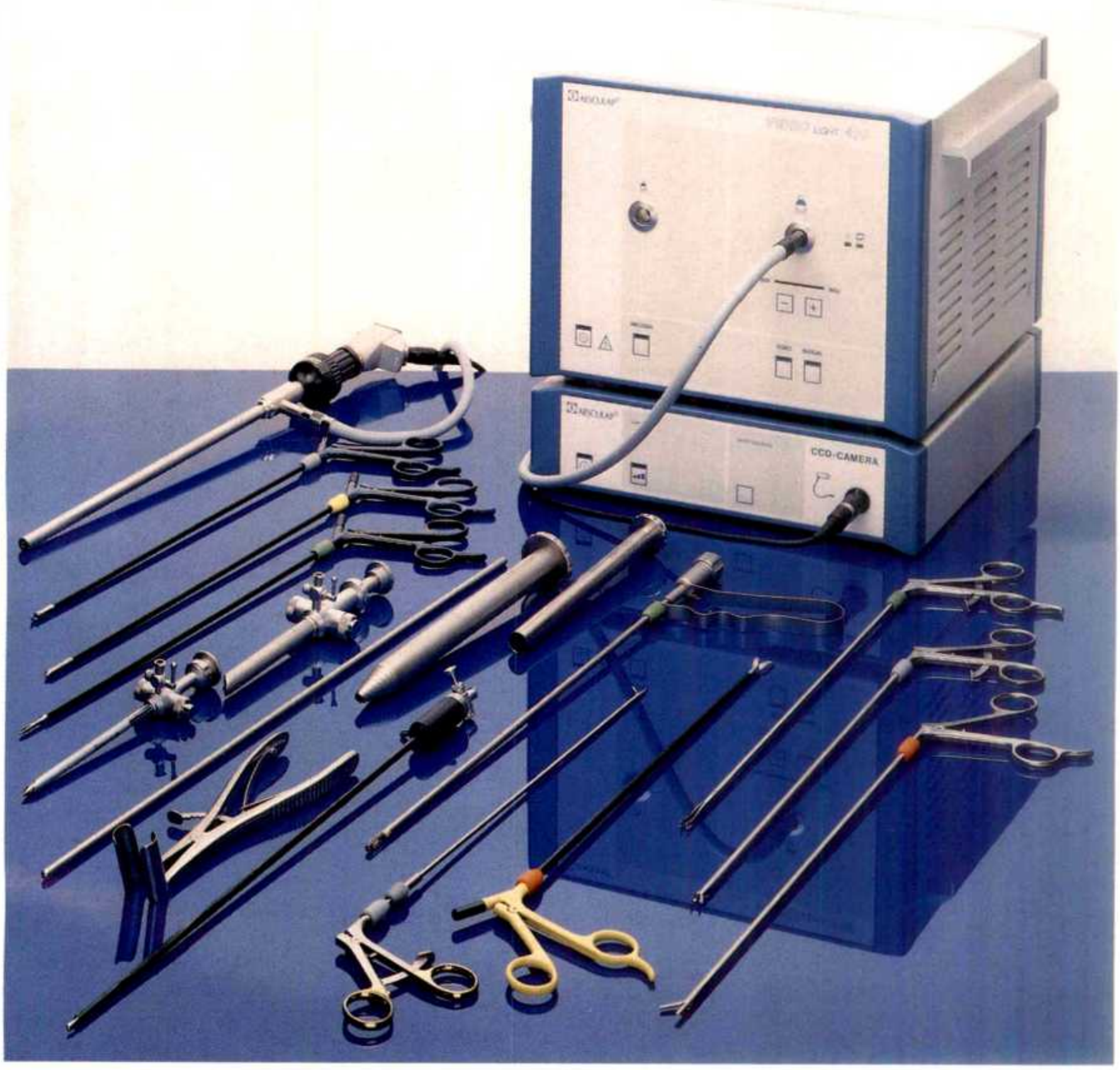

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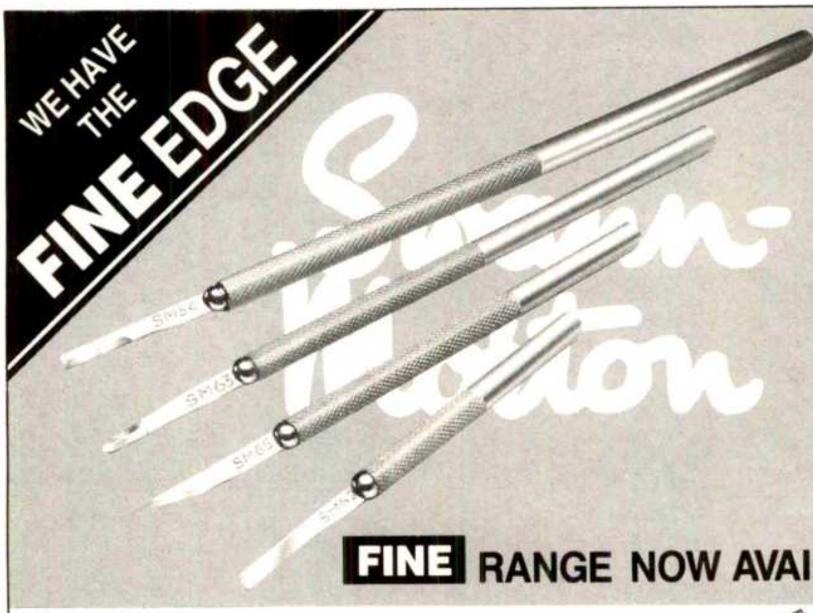

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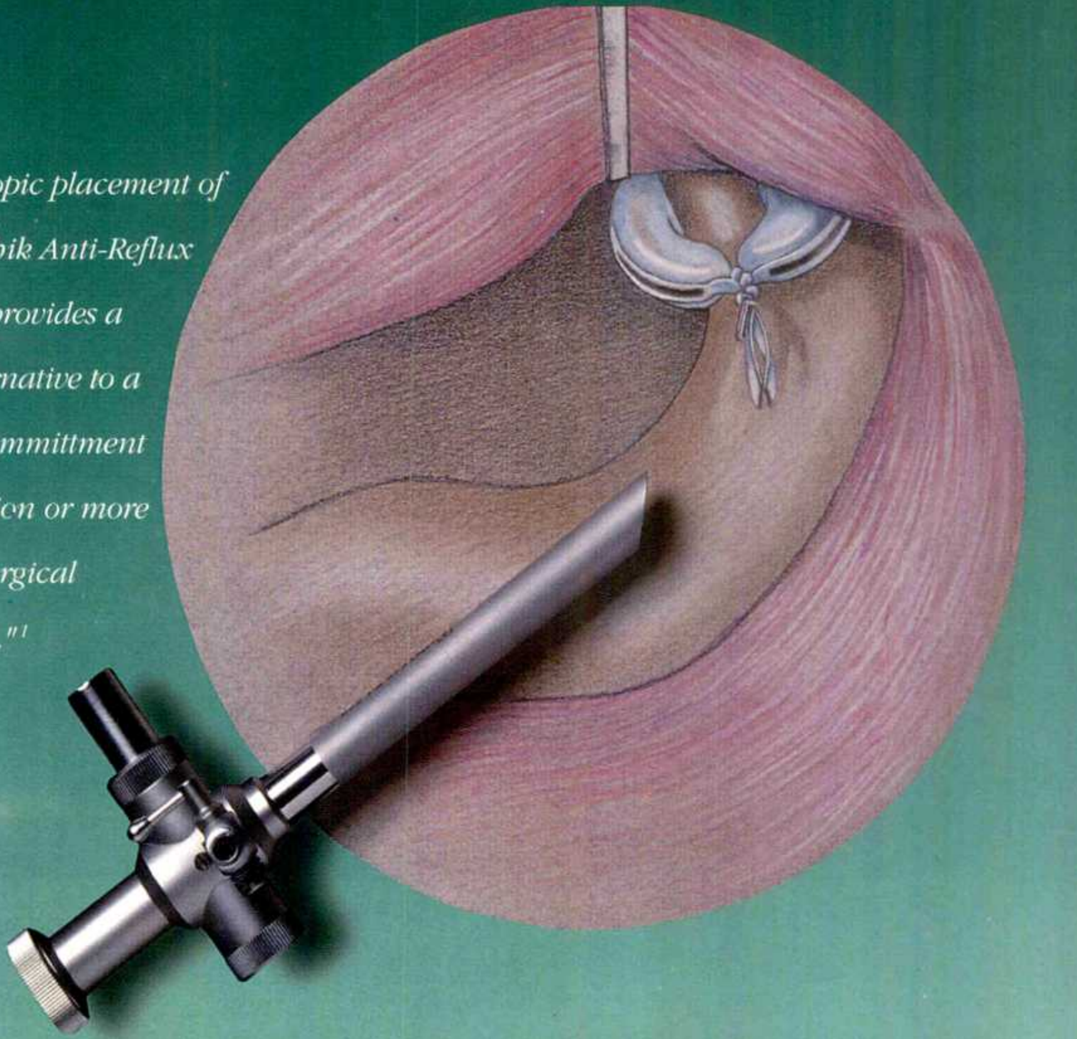

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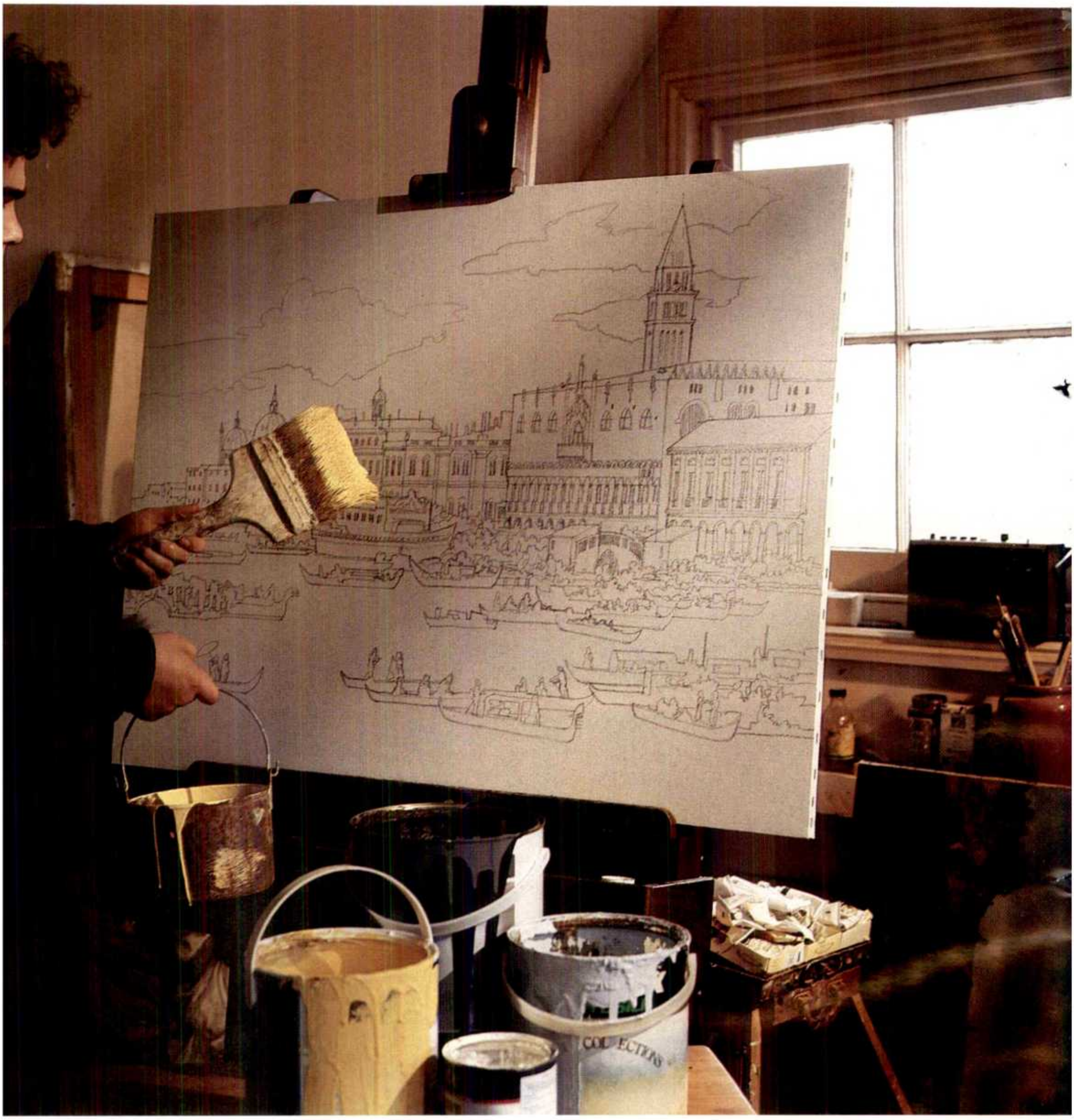

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Br. J. Surg. 1993, Vol. 80, May, 545–546

We regard The British Journal of Surgery *as a truly international journal and are proud of the strong overseas representation on the Editorial Board. Indeed, the British Isles contingent is outnumbered by representatives from the rest of the world. The Journal has always had close links with the United States of America and the British Commonwealth, but during recent years we have greatly strengthened our representation from Europe. We have also incorporated Members from a number of other countries that were not previously represented on the Board. Many of these Members act as referees for papers submitted to the Journal. In addition, they encourage potential authors and subscribers within their countries of origin and are available to advise on marketing opportunities, foreign-language editions and the like. Included on the Board are the Editors of the four journals with which we now exchange abstracts or digests:* Surgery, The American Journal of Surgery, Der Chirurg *and* Surgery Today (The Japanese Journal of Surgery). *We start this month with brief 'biosketches' of the overseas Members of the Editorial Board.*

PROFESSOR YOSHIO MISHIMA

(Japan)

Yoshio Mishima (born 1931) is Professor and Chairman of the Second Department of Surgery, Tokyo Medical and Dental University, Japan. His surgical training in Tokyo was punctuated by a 2-year attachment to the Department of Surgery in Cologne, Germany. His main clinical interest is abdominal surgery, including vascular surgery. He was President of the Japan Surgical Society in 1993 and is Editor-in-Chief of *Surgery Today* (formerly *The Japanese Journal of Surgery*).

PROFESSOR HENRI BISMUTH

(France)

Henri Bismuth (born 1934) is Professor of Surgery at Paris South University and Head of the department of surgery at Paul Brousse Hospital, Villejuif, France. His professional career has been confined largely to Paris, but his reputation in hepatobiliary surgery is worldwide. He is an Honorary Fellow of surgical colleges in Ireland, Scotland and the USA, and a member of several international societies and editorial boards. He was President of the International Hepato-Biliary-Pancreatic Association in 1984 and is current President of the European Association of University Surgeons.

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DR STANLEY GOLDBERG
(U S A)

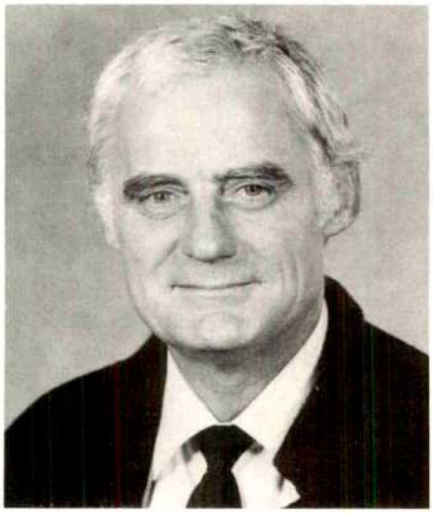
Stanley Morton Goldberg was born (in 1932) and educated in Minneapolis, Minnesota, where he has been Clinical Professor of Surgery for the past 21 years. He is Director of the Division of Colon and Rectal Surgery at University of Minnesota Medical School and was President of the American Society of Colon and Rectal Surgeons in 1983–1984. He is an Honorary Fellow of the Australasian College of Surgeons. He has written widely on many different aspects of coloproctology.

PROFESSOR JIN-POK KIM
(South Korea)

Jin-Pok Kim (born 1933) has been Professor of Surgery at Seoul National University, Korea, for the past 16 years. He graduated from Seoul in 1958. His training included clinical attachments to military hospitals in Korea and the USA, and research appointments at Boston City and Peter Bent Brigham Hospitals, Massachusetts. His interests lie chiefly in surgical oncology and immunology, and his experience of gastric cancer is virtually unparalleled. Between 1985 and 1987 he was President of the Asian Pacific Federation of Organizations of Cancer Research and Control, and also Vice-President of the International Society of Surgery.

PROFESSOR RENZO DIONIGI
(Italy)

Renzo Dionigi (born 1940) is Professor and Director of Surgery at the University of Pavia in Varese, Italy, where he has been actively involved in founding the new medical school. He trained at Pavia and then in Cincinatti, USA, where he was Assistant Professor of Research Surgery (1975–1976). In 1982 he was President of the European Society for Surgical Research. He is an Honorary Fellow of The Royal College of Surgeons of Edinburgh. His interests include nutrition of the surgical patient and oesophageal, liver and pancreatic surgery



PROFESSOR LEIF HULTÉN
(Sweden)

Leif Hultén (born 1931) is Professor of Surgery in the University of Göteborg, Sweden, and Chairman of the department of surgery at Sahlgrenska Sjukhuset, Göteborg. He is a Corresponding Fellow of The Royal College of Surgeons of England and gave the 1992 Sir Alan Parks Lecture. He is a coloproctologist with particular interests in inflammatory bowel disease, including anorectal physiology and pelvic pouch surgery.

Robin Williamson

Br. J. Surg. 1993, Vol. 80, May, 547–549

Endoscopic sphincterotomy in acute gallstone pancreatitis

Acute pancreatitis affects 6–8 per cent of all patients with symptomatic gallstones, although the proportion may be around 20 per cent in those with microlithiasis and 30 per cent in those with cholesterolosis[1]. A typical district general hospital with a catchment population of 250 000 might expect to see 30–60 new cases of acute pancreatitis each year[2]. The relative incidence according to aetiology will depend on the age profile of the population (gallstones are commoner in the elderly and in women) and the level of and susceptibility to alcohol abuse. In the Midlands region of the UK, for example, over 60 per cent of cases of acute pancreatitis are caused by gallstones[3]. Of these, 28 per cent will develop complications, which are mostly systemic. There will also be a 9 per cent incidence of symptomatic pancreatic pseudocyst, but only 4 per cent will develop significant pancreatic necrosis and only 1 per cent are likely to progress to pancreatic abscess[3]. The mortality rate will be between 8 and 15 per cent. Thus, the individual general surgeon will see relatively few patients with specific pancreatic complications. From such a perspective, the impression might be that supportive medical treatment alone will provide a good outcome in the vast majority of patients. More aggressive intervention with emergency endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy may seem, at best, a luxury and, at worst, an unnecessary interference.

This notion is, on first reflection, supported by the poor results of many retrospective series examining the role of emergency surgical biliary decompression. Moreover, classical surgical teaching states that the severity of pancreatitis is established at the instant the attack begins and cannot be altered, medical support simply tiding the patient over the systemic effects of the disease in all but the worst cases. Have there been any new developments to warrant a shift away from these viewpoints?

Surprisingly, only two randomized studies of urgent surgical intervention in gallstone pancreatitis have been performed. Kelly and Wagner[4] randomized 163 patients to undergo urgent biliary surgery within 48 h of admission or delayed surgery (after 4 days). In patients with a high Ranson score ($\geqslant 4$), the morbidity and mortality rates were significantly higher for those who underwent urgent surgery (83 and 48 per cent respectively) than for those who had delayed surgery (18 and 11 per cent). Stone *et al.*[5], however, reported a mortality rate of 3 per cent in 36 patients randomized to operation within 73 h of admission, compared with a rate of 6 per cent in 39 treated conservatively. One important difference between these two trials was that in the former the biliary tree was routinely explored supraduodenally and decompressed with a T tube, whereas Stone *et al.* always performed transduodenal sphincteroplasty.

Bile duct stone passage has been linked to the initiation of acute pancreatitis since the work of Opie at the turn of the century[1]. Recent evidence has shown that obstruction at the ampulla of Vater from an impacted stone (which is unusual), transient obstruction due to repeated passage of small stones, or intermittent obstruction by larger stones may be associated with an increasing severity of pancreatitis[1,6,7]. Experimental work in the opossum has also demonstrated the importance of pancreatic duct outflow obstruction in the progression of pancreatitis and, of equal importance, in the stabilization and even improvement of pancreatitis on release of the obstruction (M. Steer, personal communication).

Three randomized trials of urgent biliary decompression by endoscopic sphincterotomy (ES) have all shown it to be beneficial. In the Leicester study involving 121 patients, ERCP performed within 72 h of admission (plus ES if bile duct stones were present) resulted in a significant overall reduction in the morbidity rate (12 per cent) compared with conventional treatment (24 per cent)[8]. Although the trial was not designed to detect differences in mortality rate, the trend was in favour of sphincterotomy (2 *versus* 8 per cent). The outcome was similar in patients with a predicted mild attack irrespective of treatment (morbidity rate 12 per cent, mortality rate zero) but was much improved when ES was performed in patients with a predicted

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severe attack (morbidity rate 24 *versus* 61 per cent; mortality rate 2 *versus* 18 per cent). Patients who underwent sphincterotomy in the clinically severe group were also discharged a median of 8 days earlier than those who had conventional treatment. In the second trial, from Hong Kong, 195 patients were randomized to ERCP with or without ES as in the Leicester study, but the procedures were performed within 24 h and control patients had ERCP with or without sphincterotomy if they deteriorated (S.-T. Fan, personal communication). There was a non-significant reduction in mortality rate in the former group (5 *versus* 9 per cent) and a significant reduction in 'biliary sepsis' (zero *versus* 12 per cent). Unlike the Leicester study, there was no notable trend in the reduction of other systemic or local pancreatic complications. The third trial comes from Katowice in Poland, where 250 patients underwent upper gastrointestinal endoscopy within 24 h of admission (A. Nowak, personal communication)[9]. Sixty-two patients had a bulging ampulla, indicating an impacted stone, and all subsequently underwent ERCP and ES; the other 188 with a normal ampullary appearance were randomized to ES or conventional treatment. The morbidity and mortality rates were both significantly reduced in patients who underwent sphincterotomy (morbidity rate 14 *versus* 34 per cent; mortality rate 1 *versus* 11 per cent).

The latter two trials warrant further comment. Chinese patients from Hong Kong tend to have large soft primary duct stones, often without gallbladder stones, in contrast to the multiple small (and larger) cholesterol stones of gallbladder origin seen in non-Asian patients with acute pancreatitis. This may indicate a different natural history of the disease. The Katowice trial was composed largely of tertiary referrals, so that the mean delay between the time of onset of symptoms and treatment was 3–4 days. This suggests that ES is of benefit even if treatment is unavoidably delayed, although the earlier the intervention the better.

Worldwide, there have been over 1100 reported cases of ES in acute pancreatitis, with an overall mortality rate <2 per cent and a morbidity rate <6 per cent, with very few procedure-related deaths[1]. There is now good evidence to support the routine use of ERCP and ES in the following situations[1]:

1. Any patient with severe gallstone pancreatitis should undergo ERCP as soon as possible, with ES for those with bile duct stones. Although not specifically proven to be of benefit, many units now reasonably perform sphincterotomy in all cases because of the likely passage of further stones from the gallbladder and the presence of small stones and sludge in the bile duct which may not be seen during ERCP.
2. Any patient with 'mild' pancreatitis who fails to improve should have ERCP, with ES depending on the findings.
3. Any patient who requires surgery for local pancreatic complications, such as necrosis, requires ERCP with or without ES, because biliary exploration at surgery is hazardous in such circumstances and is usually impossible anyway.
4. ES may be an alternative to cholecystectomy in the prevention of further attacks of pancreatitis in frail elderly patients who may be at significant risk from abdominal surgery.

An important indicator of gallstone-related pancreatitis is an admission serum alanine or aspartate aminotransferase level $\geqslant 60$ units/l if ultrasonography has not been helpful[10], while a raised serum bilirubin level on admission, especially if $\geqslant 40$ µmol/l, is a strong indicator of 'persisting' bile duct stones[7]. Even though a benefit has not been directly proven (nor is it likely to be), the routine use of antibiotics in patients with gallstone pancreatitis is probably warranted[1].

The endoscopist who performs ERCP and sphincterotomy in patients with acute pancreatitis should avoid excessive manipulation of the ampulla of Vater and should be skilled at therapeutic biliary intervention. The true benefits of ES may be substantial, provided the procedure is integrated with a modern approach to the management of systemic and local complications, such as pancreatic necrosis. It is evident that the management of severe and complicated cases of acute pancreatitis should be coordinated by a surgeon who is a specialist in pancreatic disease[11].

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Announcement

Eurosurgery '93

The 3rd European Congress of Surgery under the auspices of Eurosurgery will take place in London from 14 to 17 September 1993. This international congress embraces all the specialties within surgery and sessions will be sponsored by all of the surgical specialist associations and societies of the participating nations, ensuring that there will be an international and multidisciplinary approach to many common surgical problems. Additionally, there will be European symposia of general interest to all surgeons on themes such as endoscopy, management of patients with trauma, daycase surgery, graduated patient care, surgical audit and surgery in the developing world. A major session on surgical training is also being organized by the surgical trainees' associations.

A large number of free papers will also be given and these communications will be published in a special supplement of *The British Journal of Surgery.*

On 14 September 1993 a number of satellite sessions sponsored by companies are being organized for delegates.

Further details and registration forms may be obtained from the Congress Secretariat, Eurosurgery 1993, Conference Associates and Services Ltd, Congress House, 55 New Cavendish Street, London W1M 8RE, UK. Telephone: 071 436 0531. Facsimile: 071 935 7559.

J. P. S. Lumley

Br. J. Surg. 1993, Vol. 80, May, 550–551

Laser angioplasty

The use of fibreoptic delivery of laser energy to vaporize occluding atheromatous material within arteries was first described[1] in 1981. Thereafter, the clinical feasibility of percutaneous laser recanalization of occluded femoropopliteal arteries in humans[2] was demonstrated in 1984. The past decade has seen the development of dedicated vascular lasers and catheter systems of ever-increasing sophistication and expense. But does laser angioplasty really work? Which laser system is most suitable? What are the indications for its use? What are the long-term results and how do they compare with those of conventional balloon angioplasty or surgical bypass?

Early attempts at laser angioplasty were made using bare optical fibres (200–600 μm in diameter) and continuous-wave argon or neodymium yttrium–aluminium–garnet (NdYAG) medical lasers. There was a high incidence of mechanical and laser-induced vessel perforation and the fibre created only an inadequate narrow channel through the lesion[3]. Development has occurred in two main areas: the use of modified fibre tips[4] such as metal-capped ('hot-tip') or transparent artificial sapphire-tipped fibres, and the application of pulsed lasers. Modified fibre tips (laser probes) are less traumatic to the vessel wall and produce a wider neolumen than bare optical fibres. Nevertheless, when used with continuous-wave medical lasers, these devices still cause some degree of thermal injury to the surrounding vessel wall. However, pulsed lasers (e.g. pulsed NdYAG, dye and excimer types) produce minimal thermal injury to the vessel wall compared with continuous-wave lasers[5] and, on the assumption that this might be clinically beneficial, their investigation and use for endovascular recanalization has become more extensive.

The use of laser angioplasty, either as an adjunct to or instead of balloon angioplasty, has two potential advantages over conventional treatment. The major possible advantage is that occlusive lesions previously amenable only to treatment by surgical bypass may be treatable by a minimally invasive technique. The second possible advantage is that, because occluding material is removed (debulked) rather than simply displaced, the restenosis rate after laser angioplasty may be less than that associated with balloon angioplasty alone in lesions where the latter is technically possible. This has been demonstrated in atherosclerotic animal models[6] but there is, as yet, no good evidence that this is the case in humans, despite such suggestions by proponents of laser thermal angioplasty. The demonstration of benefit in terms of reduced restenosis requires a long-term prospective randomized trial of laser *versus* conventional angioplasty. Such trials are in progress but, until their results become available, there is no justification for using laser angioplasty in stenotic segments or short occlusions through which a guidewire can be passed easily and balloon dilatation performed with good long-term results.

Of particular interest to vascular surgeons is the patient with a long femoropopliteal occlusion (>10 cm) for which the primary success rate of mechanical (guidewire) recanalization and balloon dilatation is relatively low[7]. Although immediate technical results are continually improving with increasing radiological expertise and the development of hydrophilic 'slippery' guidewires, even when primary guidewire recanalization and balloon angioplasty are possible, the long-term patency rate is generally poor[8,9]. For such long lesions a safe and effective minimally invasive alternative to surgical bypass would be of immense benefit. Because laser angioplasty is less invasive than surgery, its use might be justifiable in patients with a long occlusion whose symptoms may not warrant surgical intervention, for instance moderately restricting intermittent claudication, or it might be an alternative to the conventional choice of surgery for severe claudication and critical ischaemia.

But do the results of peripheral laser angioplasty justify its use? Unfortunately, the literature is clouded with numerous uncontrolled and often anecdotal studies. Consequently, clinical results appear to vary widely. Strict comparisons cannot be drawn from these reports because there is a huge variation in terms of lesion length and type (stenosis or occlusion), indications for treatment, use of percutaneous or open access and performance of additional surgical procedures at the time of angioplasty, use of anticoagulants, methods and length of follow-up, and the way in which results are reported. There are no properly randomized controlled studies comparing laser recanalization with conventional balloon angioplasty or bypass surgery, nor are there adequate comparisons of the results obtained with different

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lasers and delivery devices. However, most clinical trials have in common a relatively high initial (technical and clinical) success rate of 60–90 per cent regardless of the type of laser system and delivery device used. There is a general impression that delivery systems allowing direct laser–tissue interaction have a higher primary success rate than purely thermal (metal) devices. Calcified lesions remain a problem, even with pulsed lasers. In most series, adjunctive balloon dilatation is still required after laser recanalization to widen the resulting lumen (i.e. laser-assisted balloon angioplasty as opposed to laser angioplasty alone). A fundamental problem with most devices remains the lack of a suitable guidance system. The laser probe tends to take the line of least resistance, which is frequently within a dissection plane rather than the true arterial lumen. Poor run-off is often cited as a cause of failure after laser angioplasty, just as it is following surgical femoropopliteal bypass.

Although the primary technical success rate for long occlusions, particularly calcified lesions, could be improved, the major difficulty is maintaining patency of the vessel after recanalization. To this end, further research is needed to improve laser delivery and guidance, such that vaporization of occlusive material is maximized and the mechanical 'Dotter' effect minimized. The need for concomitant balloon dilatation must be removed to reduce the overall vascular injury and, hopefully, the risk of restenosis and reocclusion. The role of other new endovascular techniques, such as atherectomy and stenting, and drugs used in combination with lasers also needs to be evaluated.

With regard to safety, the risk of severe complications requiring surgical intervention is low and appears to be no greater than with conventional balloon angioplasty alone (around 0·7 per cent in claudicants[10]), as is the risk of limb loss as a direct consequence of laser angioplasty (about 0·1 per cent). In the light of this, the decision to use laser angioplasty will depend on the individual vascular surgeon's expectation of success. There is no doubt that some patients benefit from percutaneous laser angioplasty but, at present, although short-term results are promising, long-term results are not universally good enough to justify widespread routine application of the technique or commitment of financial resources. What is clear is the overwhelming need for randomized controlled clinical trials in centres dedicated to improving laser devices and their application in occlusive peripheral vascular disease.

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Review

Br. J. Surg. 1993, Vol. 80, May, 552–569

Laparoscopic cholecystectomy

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After laparoscopic cholecystectomy, the patient can expect a hospital stay of <2 days and a return to work within 2 weeks. The associated operative mortality rate is low at <0·2 per cent. The increased incidence of bile duct injury with the laparoscopic technique compared with open cholecystectomy is a cause for concern but such injuries should decrease with proper training in laparoscopic surgery. The use of operative cholangiography (whether routine, selective or never) is controversial but there is no evidence that routine cholangiography will prevent major bile duct injury.

Since the first successful laparoscopic cholecystectomy in 1987, the operation has been accepted into general surgical practice more rapidly than any other new procedure. It is already well established in the UK[1].

The popularity of laparoscopic cholecystectomy can be attributed largely to benefits for the patient, but there are also advantages for society in reduced loss of work following a commonly performed procedure. In addition, the operation has introduced general surgeons to therapeutic laparoscopy and thus paved the way for other minimally invasive procedures within the abdomen and chest. The new operation is not, however, without problems, in particular the apparent increase in damage to the extrahepatic bile ducts. Nor is it free from controversy: surgeons remain divided about the place of operative cholangiography and the treatment of duct stones.

In this review the history of laparoscopic cholecystectomy is outlined briefly and the published literature examined, looking in particular at resource implications, results and implications for training.

Historical perspective

Cholecystectomy was first performed by Langenbuch[2,A1]* in Berlin in 1882. Some 20 years later Kelling[3] pioneered diagnostic laparoscopy in dogs using a cystoscope. Jacobeus[4] of Stockholm is credited with the first laparoscopy in humans in 1911. By the 1930s carbon dioxide was in use for pneumoperitoneum and a spring-loaded needle, designed by Veress[5] for therapeutic pneumothorax, was modified for the safe introduction of gas into the abdomen. Gynaecologists in Europe began to use laparoscopy regularly for diagnosis and tubal diathermy in the 1960s.

Therapeutic endoscopic abdominal and pelvic surgery was powerfully championed by Semm[6]. Having developed instruments and techniques for gynaecological procedures such as tubal diathermy, ovarian biopsy and pelvic adhesiolysis[7], he performed the first laparoscopic appendicectomy[8] in 1983, the same year as Mouret in France. Berci and Cuschieri[9] advocated both diagnostic and therapeutic laparoscopy (including cholecystostomy) for a variety of gastrointestinal problems[10]. Ko and Airans in Chicago, using a canine model, and Cuschieri and Nathanson in Dundee, working on the pig, independently explored the technique of laparoscopic cholecystectomy. Mouret, drawing on experience with gynaecological operations and appendicectomy, is generally credited as having performed the first laparoscopic cholecystectomy in humans in 1987[A2]. By the following year several groups were independently developing the technique: Dubois *et al.*[11] in Paris, Perissat and colleagues[12] in Bordeaux, Reddick and Olsen[13] in Tennessee, and McKernan[14] in Georgia. In 1989 Cuschieri and coworkers[15] in Dundee performed the procedure for the first time in the UK.

Laparoscopic cholecystectomy as the standard treatment for gallbladder stones

Laparoscopic cholecystectomy has undoubtedly standardized the treatment of gallbladder stones. In a major review of the treatments available in 1991, Cheslyn-Curtis and Russell[16] discussed no fewer than seven methods (*Table 1*). It is likely that laparoscopic cholecystectomy will render all of these obsolete. Oral dissolution therapy, appropriate for only 10 per cent of patients and effective in only about half of these, may have a place for suitable patients who are unwilling or unable to undergo general anaesthesia. Extracorporeal shockwave lithotripsy, while retaining a place in the management of large common duct stones, appears to have no role in the treatment of gallbladder stones[17]. It has been advocated as a prelude to laparoscopic cholecystectomy to reduce stone size and thus make both gallstone and gallbladder extraction easier. Intracorporeal shockwave lithotripsy has also been suggested[18] but has not been widely adopted. Other percutaneous techniques that dissolve or remove stones but leave the gallbladder mucosa *in situ* are inferior treatments because of the risk of stone recurrence[19]. Langenbuch's assertion that 'the gallbladder needs to be removed not because it contains stones but because it forms them' is as pertinent today as it was over 100 years ago[2]. Laparoscopic cholecystectomy has become the treatment of choice for the vast

Table 1 *Techniques described for treatment of gallbladder stones (after Cheslyn-Curtis and Russell[16])*

Technique	Percentage suitable	Percentage effective	Remarks
Oral dissolution	10	40–60	50% recurrence rate
Extracorporeal shock-wave lithotripsy	<15	90	Recurrence?
Percutaneous cholecystostomy	—	—	—
Percutaneous transhepatic MTBE infusion	—	50–96	High morbidity rate
Percutaneous cholecystolithotomy	—	89	Recurrence?
Minicholecystostomy with later radiological stone removal	70	85	—
Minicholecystectomy	—	—	—

MTBE, methyl-*t*-butyl ether

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* *References added in proof to ensure topicality are listed in the* Addendum *and numbered A1–A9*

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majority of patients in the developed world presenting with symptomatic gallbladder stones.

Indications and contraindications

Although Dubois *et al.*[20] have extended the indications to include patients with asymptomatic gallbladder calculi, the generally accepted indications for laparoscopic cholecystectomy are the same as those for the open procedure, i.e. gallstones that cause symptoms[21]. It is difficult to assess whether surgeons have broadened the indications for laparoscopic compared with open cholecystectomy. Debate will continue about whether a prophylactic laparoscopic operation is indicated for asymptomatic stones.

Although the only absolute contraindication to open cholecystectomy is unfitness for general anaesthesia, laparoscopic cholecystectomy has had several contraindications. In the early days of the procedure Cuschieri *et al.*[22] counselled that it should not be performed in patients with acute cholecystitis, in those with morbid obesity, in situations where the gallbladder was adherent to the duct, in jaundiced patients or in the presence of known ductal calculi. As the operation developed, many of these contraindications were overcome. For example, several series have reported laparoscopic cholecystectomy in patients with complicated acute cholecystitis[23–25]. Some centres now advocate an 'all-comers' policy[26]. With the advent of longer cannulas, morbid obesity is no longer a contraindication and, indeed, the obese patient fares relatively better following laparoscopic than open cholecystectomy[27,28]. Mirizzi's syndrome has also been successfully treated laparoscopically[29]. As experience is gained with laparoscopic treatment of common duct stones, so ductal calculi are no longer a contraindication for many surgeons[30–33]. The list of generally agreed contraindications has thus now diminished to three: first, when the patient is unfit for general anaesthesia (although successful laparoscopic cholecystectomy has been reported under epidural anaesthesia[34]); second, cholecystoenteric fistula; and third, when there are doubts about gallbladder malignancy[35]. For patients who present with gallbladder stones, as opposed to ductal calculi, the operation can now be virtually universally recommended.

Resource implications

By simple calculation from manufacturers' price lists, the capital cost of setting up for laparoscopic cholecystectomy is currently £24 000–27 000. By 1993 most general surgical units in the UK will have obtained, or at least ordered, this equipment[1]. The on-going hospital cost of laparoscopic cholecystectomy can be calculated in countries whose healthcare systems provide accurate figures. The exercise is made slightly more complex when depreciation, maintenance and replacement of laparoscopic equipment, and the extent to which disposable equipment is used, are taken into account. Calculation is also made more difficult by the increased use of endoscopic retrograde cholangiopancreatography (ERCP) in many series and by variation in the rate of conversion to open operation. Economic assessment should also take account of the financial benefits to society of earlier return to work. Perhaps because of these complexities, little has been published on this topic and conflicting conclusions have been reached. Studies from the UK, Australia, Germany and the USA show lower hospital costs for laparoscopic than for open cholecystectomy[36–38,A3]. On the other hand, a study from the USA has calculated that hospital expenses for elective laparoscopic cholecystectomy are US $1000 higher than for open operation[39].

Arguably the greatest benefit for both patient and healthcare system is reduced hospital stay. Although median postoperative hospital stay is arguably the most appropriate measure, many series have reported the mean value (*Table 2*). In the United States this average is about 1 day, with the 23-h admission being particularly popular. In Europe the stay has been longer, averaging between 2 and 3 days. This figure is likely to fall as surgeons appreciate that it is rarely necessary for the patient to have a bladder catheter, an intravenous infusion, a drain or opiate analgesia after laparoscopic cholecystectomy. This is exemplified by the present authors' experience; the mean postoperative hospital stay for our first 100 patients was 2·4 days, whereas for the fourth 100 it was half this. The mean postoperative stay in the USA following open cholecystectomy[51] is 6·2 days. This figure is identical to that from a recent audit of open cholecystectomy in Lothian[52] but, in patients in whom the bile duct was explored (15–20 per cent in most published series), the mean stay increased to 14·3 days. Large-scale audit should provide more reliable data and avoid the bias inherent in series from specialist centres. Postoperative hospital stay in major audit reports is shown in *Table 3*.

Table 2 *Mean hospital stay after laparoscopic cholecystectomy in published series*

Reference	Year	No. of patients	Hospital stay (days)
Spaw *et al.*[40]	1991	500	0·98
Berci and Sackier[41]	1991	418	1·0
Peters *et al.*[42]	1991	100	1·1
Walsh[43]	1991	55	1·1
Schirmer *et al.*[44]	1991	139	1·2
Southern Surgeons[45]	1991	1518	1·2
Bailey *et al.*[46]	1991	375	1·3
Ferzli and Kloss[47]	1991	111	1·4
Grace *et al.*[48]	1991	44	1·5
Western General Hospital, Edinburgh*	1991	350	2·0
Nathanson *et al.*[15]	1991	60	2·9
Cuschieri *et al.*[49]	1991	1236	3·0
Neugebauer *et al.*[50]	1991	100	3·0

*Unpublished results

Table 3 *Mean hospital stay after laparoscopic cholecystectomy in audit series*

Source	No. of patients	Hospital stay (days)
England*	1581	2·2
Singapore†	1100	3·0
Belgium†	3244	3·9
Switzerland†	1091	4·7
Japan†	2888	7·6

*Royal College of Surgeons of England Confidential Audit (D. C. Dunn, personal communication); †published abstracts, Third World Congress of Endoscopic Surgery, Bordeaux, 1992

Resource implications for healthcare systems

The resource benefits to the healthcare system as a whole are more difficult to assess than simple postoperative hospital stay. On the credit side, shorter stay should result in reduced bed requirements and lowered costs of drugs and disposables. On the debit side, there is not only the capital cost of the instruments and equipment, but also their depreciation and maintenance, which may be considerable. The operation can be performed without use of disposable equipment but, if such equipment is employed, the cost may increase by £400 at current prices. The use of theatre time must also be considered, although this can be difficult to quantify in resource terms. With increasing surgical experience operating time has approached that of open cholecystectomy. Thus in the authors' series the mean time in the operating theatre for the first 100 patients was 107 min but this had fallen to 83 min for the fourth 100.

In an audit of the comparative cost of the two operations to the National Health Service, Fullarton *et al.*[53] calculated that laparoscopic cholecystectomy was cheaper, costing £2053 compared with £2250 for the open procedure. Kurzawinski *et*

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al.[36] calculated that open cholecystectomy cost £2085 whereas the laparoscopic operation cost £2158, reducing to £1705 if disposable cannulas and instruments were not used.

Table 4 *Time to return to full-time work after laparoscopic cholecystectomy*

Reference	Year	No. of patients	Time to return to work (days)
Cuschieri *et al.*[49]	1991	1236	11*
Wilson *et al.*[54]	1991	180	12*
Peters *et al.*[42]	1991	100	12·8*
Spaw *et al.*[40]	1991	500	5·2†
Graves *et al.*[55]	1991	304	7·2†
Nottle *et al.*[56]	1991	50	11†
Zucker *et al.*[57]	1991	100	94% within 7
Southern Surgeons[45]	1991	139	79% within 10

*Median; †mean

Resource implications for society

Laparoscopic cholecystectomy allows an earlier return to work for a group of patients who are mostly of working age. Time to return to work in the major published series is shown in *Table 4*. Return to work has tended to be faster in the USA than Europe, a trend highlighted by Vitale *et al.*[58] in a direct comparison of American and French patients. In the series of Spaw *et al.*[40] the mean time to return to work was 5·2 days, whereas in the Southern Surgeons' study[45] 79 per cent of patients had returned to work within 10 days. In Europe, the multicentre study reported by Cuschieri *et al.*[49] described a median of 11 days, Wilson and colleagues[54] reported 12 days and the present authors' experience is 14 days. This is in part a reflection of advice about return to work given by surgeons, which was presumably conservative until more experience was gained. It also may reflect the unwillingness of general practitioners to allow patients to return to work earlier after cholecystectomy, no matter how performed. As surgeons gain more experience and this is passed on to general practitioners it seems likely that the majority of patients will be able to return to work within 10 days of operation. This compares with a return-to-work time of about 6 weeks after open cholecystectomy in most published series.

Results

Rate of conversion to open cholecystectomy

In all large reported series the operation could not be completed laparoscopically in a proportion of patients. The patient can now justifiably expect from the surgeon an estimate of the likelihood of this event. Conversion rates in published series are shown in *Table 5*. Most of these series are selective, commonly excluding, for example, emergency operations. Where emergency laparoscopic cholecystectomy has been reported the conversion rate tends to be higher[24,25].

For elective surgery some have reported conversion rates as high as 14 per cent, but a commonly quoted figure is 5 per cent; many of the early series were remarkably consistent in this regard. During the learning period a high conversion rate is inevitable and should not be regarded as failure. However, as surgical experience and confidence with the procedure grow, it is likely that this rate will fall. Surgeons can ultimately expect to achieve a conversion rate $\leqslant 2$ per cent.

Operative morbidity

Bile duct injury. Injury to the bile duct requiring reconstruction causes the most serious morbidity associated with laparoscopic cholecystectomy and has an incidence of 0–2 per cent in published series (*Table 6*) and 0·5–0·9 per cent in audit reports (*Table 7*). It is difficult to calculate incidence following even open cholecystectomy because of under-reporting and because it is such an uncommon problem[68]. In the 63 252 patients reported by the Professional Activity Study Commission[69] the common bile duct (CBD) injury rate was 0·5 per cent. The most widely quoted European figures are those of Andren-Sandberg *et al.*[70] from Sweden. They recorded an annual incidence of 0·05 per cent between 1975 and 1982 and attributed this low figure to increased awareness of the problem and better surgical training compared with earlier studies.

Anecdotal reports suggest that the incidence may be higher than in published series (*Table 6*)[69,70]. Large-scale audit is potentially more likely to reflect the true scale of the problem but, at present, audit is voluntary so that even here under-reporting is probable. Most series do not report the reasons for bile duct damage, although the mechanisms of duct injury during laparoscopic cholecystectomy and its subsequent management have been described in papers from major referral

Table 5 *Rate of conversion from laparoscopic to open cholecystectomy in published series of 100 or more patients*

Reference	Year	No. of patients	Conversion rate (%)
Grace *et al.*[59]	1991	100	14·0
Schirmer *et al.*[44]	1991	152	8·5
Graves *et al.*[55]*	1991	304	6·9
Wilson *et al.*[54]	1991	180	6·0
Dubois *et al.*[20]*	1991	690	5·8
Zucker *et al.*[57]*	1991	100	5·0
Berci and Sackier[41]*	1991	418	5·0
Voyles *et al.*[60]*	1991	453	5·0
Stoker *et al.*[39]*	1992	280	5·0
Southern Surgeons[45]*	1991	1518	4·7
Davis *et al.*[61]*	1992	622	4·2
Peters *et al.*[42]*	1991	100	4·0
Cuschieri *et al.*[49]	1991	1236	3·6
Soper *et al.*[62]*	1992	6·8	2·9
Ferzli and Kloss[47]*	1991	111	2·0
Spaw *et al.*[40]	1991	500	1·8
Martin *et al.*[26]	1992	162	1·5

*Series in which patient selection was used

Table 6 *Incidence of bile duct injury and operative cholangiography in published series*

Reference	Year	No. of patients	Bile duct injury (%)	Operative cholangiography (%)
McKernan[14]	1991	50	2	0
Zucker *et al.*[57]	1991	100	2·0	31·0
Neugebauer *et al.*[50]	1991	100	1·0	n.a.
Peters *et al.*[42]	1991	100	1·0	8·0
Goodman *et al.*[63]	1991	100	1·0	76·0
Wilson *et al.*[54]	1991	180	0·6	0
Schirmer *et al.*[44]	1991	152	0·6	66·0
Southern Surgeons[45]	1991	1518	0·5	29·2
Berci and Sackier[41]	1991	418	0·5	90·0
Cuschieri *et al.*[49]	1991	1236	0·34	n.a.
Graves *et al.*[55]	1991	304	0·3	34·0
Larson *et al.*[64]	1992	1983	0·25	37·3
Soper *et al.*[62]	1992	618	0·2	24·0
Davis *et al.*[61]	1992	622	0·14	14·7
Graffis[66]	1992	900	0·12	n.a.
Voyles *et al.*[60]	1991	453	0	0
Grace *et al.*[48]	1991	100	0	0
Western General Hospital, Edinburgh*	1991	400	0	10·5
Spaw *et al.*[40]	1991	500	0	79·0
Perissat *et al.*[18]	1991	104	0	0
Ferzli and Kloss[47]	1991	111	0	21·0
Martin *et al.*[26]	1992	162	0	44·0
Wolfe *et al.*[65]	1991	381	0	n.a.
Dubois *et al.*[20]	1991	690	0	0

n.a., Not stated in publication; *unpublished data

Table 7 *Incidence of bile duct injury in audit series*

Audit	No. of patients	Bile duct injury (%)
USA*	1 771	0·2
England†	2 131	0·3
Switzerland‡	1 091	0·46
Belgium‡	3 244	0·5
Deziel *et al.*[67]	77 604	0·59
Singapore‡	1 100	0·9
Japan‡	2 888	0·9

*Society of American Gastrointestinal Endoscopic Surgeons survey; †Royal College of Surgeons of England confidential audit (D. C. Dunn, personal communication); ‡published abstracts, Third World Congress of Endoscopic Surgery, Bordeaux, 1992

centres in the USA[73–75]. These reports emphasize that major bile duct injury commonly goes unrecognized at the time of the primary procedure[73–75], in some instances being appreciated only following conversion to an open operation. Heightened awareness of the problem may increase peroperative recognition of such injury. Thus, Deziel and colleagues[67] have more recently reported 459 injuries in 77 604 procedures. In the 162 instances for which information about timing was available, the injury was recognized during operation in 49 per cent. Following unrecognized major duct transection there may be diffuse abdominal pain, anorexia and abdominal distension that precede the onset of jaundice in the early postoperative period[74,75]; in such patients early ERCP is the investigation of choice. A second group of patients presents later with progressive obstructive jaundice, resulting from benign stricture of the common hepatic duct[64,75]. The exact mechanism for this is uncertain, but it most probably results from excessive dissection of the ducts compromising the blood supply[76] or from the injudicious or excessive application of an energy source around the duct[73].

Hunter[77] has suggested that bile duct injury can be avoided by routine use of a 30° laparoscope, maintaining firm cephalic traction on the fundus of the gallbladder, lateral traction on the infundibulum of the gallbladder to place the cystic duct as near perpendicular to the bile duct as possible, and routine operative cholangiography.

The value of dissection close to the neck of the gallbladder, with dissection away from rather than towards the gallbladder, has been emphasized[74,75]. However, the use of routine operative cholangiography to clarify duct anatomy remains controversial. Most authors reporting series of bile duct injury recommend operative cholangiography either routinely or where there is doubt about anatomy. Yet Sackier *et al.*[78], leading advocates of routine cholangiography, in a series of 464 cases converted 12 patients to open operation because of findings on cholangiography, only eight of whom had CBD stones. In two cases conversion was required for bile duct injury that occurred during or after cholangiography; a further two patients had unnecessary conversions because of failure to visualize proximal bile ducts that were in fact intact. Gregg[79], reporting a series of 2533 open cholecystectomies, had a single common duct injury caused by attempting to obtain a cholangiogram in a patient with a small CBD. Operative cholangiography may also be performed too late to avoid biliary injury. In the review of Andren-Sandberg *et al.*[70] bile duct injury occurred before operative cholangiogram films were seen in 43 per cent of patients and after they were seen in a further 53 per cent. Furthermore, there may be a tendency to use operative cholangiography as a substitute for meticulous and time-consuming dissection of ductal anatomy. Operative cholangiograms can be difficult to interpret and are subject to considerable observer variation[80]. Dubois and co-workers[20], who do not perform routine operative cholangiography, have had no major bile duct injury in 640 patients and, in the present authors' experience when a policy of selective cholangiography has been used, there has been no major bile duct injury in over 400 patients. Andren-Sandberg *et al.*[70] demonstrated that most bile duct injuries occurred when the surgeon had performed between 25 and 100 open cholecystectomies. Ten of the 12 bile duct injuries in the series of Davidoff *et al.*[75] occurred during the first 12 cases. A similar relationship between surgical inexperience and bile duct injury was reported in two large prospective series[45,64] and confirmed by a recent multicentre national survey in the USA[67]. Larson *et al.*[64] concluded that bile duct injury correlated more with surgical inexperience than with a particular policy of cholangiography. The present review of published series confirms this assertion; there was no correlation between the incidence of bile duct injury and the frequency of operative cholangiography (*Table 6*).

It is to be hoped that the incidence of bile duct injury will decrease as surgeons gain experience, but this major complication alone emphasizes the need for adequate training in laparoscopic cholecystectomy. The opinion of Blumgart *et al.*[76] remains as relevant to laparoscopic as it was to open cholecystectomy:

> 'bile duct strictures at cholecystectomy are inflicted as a result of imprecise dissection and poor visualization of anatomical structures'.

Bile leaks. Postoperative biliary fistula and bile collection have been reported following laparoscopic cholecystectomy. Some have been due to failure of clips used to secure the cystic duct[20,65,81,82], others to fistula after common hepatic duct injury, as in the series of Dubois *et al.*[20] in which two patients presented with a small fistula thought to be secondary to diathermy injury. A third reported source of bile leak following laparoscopic cholecystectomy is from the accessory ducts of Luschka[14,42,54,62,65]. The majority of these complications have been dealt with by laparotomy, although some have used percutaneous drainage combined with endoscopic biliary drainage[18,20,59,64,65,81]. Laparoscopy for peritoneal lavage and placement of a subhepatic drain has also been reported[18].

Visceral and vascular injury. Diagnostic laparoscopy has a small but well documented incidence of both visceral and vascular injury estimated at 0·3–2 per cent[83,84]. Inevitably, such injuries have occurred during laparoscopic cholecystectomy. To avoid such problems the routine use of open laparoscopy has been advocated[14], although even this is not free from bowel injury[62]. Bowel injury at laparoscopy has been widely reported[40,45,54,61–64,67,85] with approximately half being caused by trocar or Veress needle insertion and the remainder during dissection of abdominal or gallbladder adhesions. When recognized during the procedure, these injuries have generally been repaired by laparotomy without serious adverse effects. Injuries that go unrecognized at laparoscopy carry high rates of morbidity and mortality[65,85], presumably because early postoperative discharge results in delay in presentation and diagnosis.

Major vascular injury also occurs but is fortunately rare[47,64,67,85]; 36 such injuries (0·05 per cent) were reported by Deziel *et al.*[67], of which three proved fatal.

Operative mortality

The reported operative mortality rate of open cholecystectomy in recent series ranges from 0·6 to 1·7 per cent[86,87]. In Lothian[88], the mortality rate following 6700 open cholecystectomies between 1980 and 1988 was 0·6 per cent for cholecystectomy alone and 0·9 per cent when exploration of the CBD was included; deaths were virtually confined to those aged over 60 years. The operative mortality rate for laparoscopic cholecystectomy has been low in reported series, with no death in the largest European study[49] to date and only one death in the Southern Surgeons' series[45] (the result of misdiagnosis, the patient dying from an undiagnosed leaking abdominal aortic aneurysm). In the series reported by Dubois *et al.*[20] the only death in 690 patients (0·14 per cent) was from pulmonary embolism. Wolfe *et al.*[65] reported three deaths in a series of 381 procedures (0·8 per cent), of which two were caused by bowel injury. The confidential audit[89] by The Royal College of Surgeons of England has reported a mortality rate of 0·12 per cent in 1581 patients, four times less than following open cholecystectomy (D. C. Dunn, personal communication). Deziel and colleagues[67] reported 33 postoperative deaths (0·04 per cent) in their large audit, 18 (0·02 per cent) of which were related to iatrogenic intraoperative injury. As ever, confidential audit series are likely to give a more accurate reflection of mortality rate than reported series, which tend to be smaller and suffer from the bias of 'positive reporting'.

Symptomatic outcome

There are few published data on symptomatic outcome following laparoscopic cholecystectomy. Peters *et al.*[42] reported a 3-month follow-up of 52 patients of whom 77 per cent considered their symptoms improved. In the present authors' survey of 100 patients 1 year or more after laparoscopic cholecystectomy there was no significant difference in symptomatic outcome compared with that after the open operation[90]; the proportion of patients who regarded themselves as cured (94 per cent) and who felt the procedure to have been a success (95 per cent) was identical for each type of operation.

Areas of controversy

Laser dissection

Concern has been expressed that in its early days the move to laparoscopic cholecystectomy was driven by commerce rather than science. The medical laser companies were certainly active in promoting the new operation and attempted to establish the laser as an integral part of it. In the UK many of the early meetings and training courses were organized by these companies. Such promotion has become less effective with the publication of clinical studies that have shown no advantage for laser over electrosurgical dissection[64,91]. This, together with the development of better electrosurgical dissectors and scissors, has resulted in a move away from routine laser dissection in the United States. The suggestion that bile duct injury may be associated with use of laser dissection[92] cannot be confirmed or refuted from the literature.

Lack of a large-scale controlled trial

The lack of a large-scale controlled trial comparing open and laparoscopic cholecystectomy is now a matter of history. In this country the Medical Research Council and in Germany a large multicentre group[50] tried and failed to mount a controlled trial, and the opportunity has now been lost. The reasons for this are easy to find. Simple audit rapidly demonstrated the shorter hospital stay and reduced time off work associated with the laparoscopic procedure. Perhaps most important of all was that surgeons, seeing patients on the morning after laparoscopic cholecystectomy, could not fail to be impressed with the patients' feeling of wellbeing and relative lack of pain. In these circumstances a clinical trial became unethical for most surgeons. The small randomized controlled trials that have been reported have compared laparoscopic with minicholecystectomy and have invariably found in favour of the former[A4,A5]. Although always to be regretted, the lack of controlled trials to substantiate a new technique in surgery is not new; indeed, operations introduced on the basis of a prospective randomized trial are the exception rather than the rule.

Training for laparoscopic cholecystectomy

The English[93] and Australasian[94] Surgical Colleges, and the influential Society of American Gastrointestinal Endoscopic Surgeons[95] in the USA have all made recommendations on training for the technique. In summary, these are that the surgeon performing laparoscopic cholecystectomy should be a trained general surgeon with biliary experience, should have knowledge of diagnostic laparoscopy, and should attend a course or workshop, preferably one offering hands-on experience. In addition, the English College recommend visiting a centre where the technique is already established. It is difficult to judge the extent to which these guidelines have been followed and whether failure to adhere to them has produced bad results. A survey of UK consultant general surgeons[1] showed that, although nearly 99 per cent felt that specific training was necessary, almost 20 per cent were self-taught. About one-third would have liked more training before starting laparoscopic cholecystectomy. Teaching of this operation has now moved to a more conventional footing with consultants training junior staff (or in some cases vice versa). In the UK survey of laparoscopic cholecystectomy practice[1] only 40 per cent of consultants performing cholecystectomy had previously performed laparoscopy regularly. The survey further showed that 85 per cent of consultants who responded either performed laparoscopic cholecystectomy or planned to introduce it. Only 15 of the 103 who did not intend to introduce it were not convinced of its value; the rest considered themselves too old or too specialized in other areas to make learning the technique worthwhile.

Bile duct stones

The diagnosis and treatment of bile duct stones remains controversial. The debate begins with the question of whether operative cholangiography should be performed routinely or selectively, or whether it should be performed at all. When laparoscopic cholecystectomy was introduced, techniques for laparoscopic choledochotomy were not available whereas those for endoscopic treatment of bile duct stones were increasingly being used with good effect[96]. A policy that attempted to diagnose and treat bile duct stones before surgery was, therefore, logical. It now seems to be generally agreed that every surgeon undertaking laparoscopic cholecystectomy should develop the technical expertise to perform operative cholangiography. Authorities such as Berci *et al.*[97] and Hunter[77] have advocated routine operative cholangiography both to delineate biliary anatomy and to diagnose bile duct stones. Assuming that all surgeons performing laparoscopic cholecystectomy have learned the technique of operative cholangiography, should it be used routinely, selectively or at all to diagnose bile duct stones? Laparoscopic cholecystectomy differs from the open technique in that stones diagnosed by cholangiography during the latter are better removed during operation; this cannot yet be said for laparoscopic cholecystectomy as techniques of laparoscopic exploration of the CBD and choledocholithotomy have not been widely adopted. Although well described[98], there is insufficient information in the literature about the results to recommend their routine use. Laparoscopists performing routine cholangiography are, therefore, faced with a dilemma when they diagnose unexpected duct calculi. Should the operation be converted to an open one to allow bile duct exploration, thereby negating the benefit of the laparoscopic technique in this higher risk group of patients, or should the patient be treated by postoperative ERCP and papillotomy? The risk of the latter policy is that postoperative endoscopic stone extraction may be a technical failure. Furthermore, there may be long-term sequelae from endoscopic papillotomy, especially in younger patients[99].

It can be argued that there is even more evidence to support the selective use of cholangiography at laparoscopic cholecystectomy than during the open technique. Gerber and Apt[100] felt that a policy of selective cholangiography is preferable on grounds of cost, operative time and successful outcome as measured by a virtual absence of subsequent duct stones on 5-year follow-up. The incidence of subsequent symptomatic duct stones in large series of open cholecystectomy without cholangiography has been as low as 0·3 per cent. The diagnosis of bile duct stones before operation has been greatly enhanced

Table 8 *Laparoscopic cholecystectomy series using operative cholangiography selectively or never*

Series	No. of patients	Operative cholangiograms	Preoperative ERC		Postoperative ERC	
			Total	Sphincterotomy	Total	Stones
Middlesex Hospital, London*	434	0 (0)	52 (12·0)	23 (5·3)	16 (3·7)	6 (1·4)
Johns Hopkins, Baltimore[A6]	400	8 (2·0)	44 (11·0)	14 (3·5)	6 (1·5)	3 (0·8)
Whipps Cross Hospital, London[A7]	522	0 (0)	73 (14·0)	26 (5·0)	n.a.	4 (0·8)
Western General Hospital, Edinburgh†	400	17 (4·2)	81 (20·2)	31 (7·8)	17 (4·2)	8 (2·0)
Royal Brisbane[A8]	600	26 (4·3)	29 (4·8)	10 (1·7)	9 (1·5)	5 (0·8)
Washington University, St Louis[A9]	326	76 (23·3)	31 (9·5)	18 (5·5)	2 (0·6)	2 (0·6)
Beaumont, Dublin[103]	375	5 (1·3)	53 (14·1)	13 (3·5)	17 (4·5)	4 (1·1)

Values in parentheses are percentages. ERC, endoscopic retrograde cholangiography. *R. C. G. Russell, personal communication; †unpublished data; n.a., not stated in publication

by the widespread availability of ultrasonography and ERCP; it has been further enhanced by improved contrast agent for intravenous cholangiography, which has virtually abolished hypersensitivity reactions and yields good-quality images[101]. Scott-Coombes and Thomson[102] have presented the case for selective cholangiography with laparoscopic cholecystectomy. A recent assessment of current evidence[A5] found in favour of a selective policy. The criteria for selection for cholangiography have varied. Commonly, any one of a history of jaundice or pancreatitis, abnormal liver function tests or amylase, and dilatation of the biliary tree on ultrasonography is regarded as an indication. The use of such a policy will result in 'very few' duct stones being missed[A5] and there is debate about the clinical significance of those that are: small stones can frequently pass spontaneously. The results of series that have employed a 'selective' or 'never' policy are shown in *Table 8*. A policy of selective use of preoperative and postoperative endoscopic retrograde cholangiography has therefore been successful in the management of duct stones in several major centres from around the world. Refinement of the indications for cholangiography should improve the efficiency of this policy still further.

Advocates of routine cholangiography acknowledge that routine operative cholangiography will produce false-positives resulting in unnecessary duct exploration. Whether the rate of these will be higher or lower than the 3–9 per cent reported for open cholangiography remains to be seen. Our survey[1] showed that about two-thirds of British surgeons employ a selective cholangiography policy with laparoscopic cholecystectomy. The debate seems destined to continue.

Conclusions

Laparoscopic cholecystectomy has become the treatment of choice for patients presenting with gallbladder stones. The patient can anticipate a hospital stay after operation of <2 days, without a postoperative intravenous infusion and without opiate analgesia. The increased incidence of bile duct damage remains a source of anxiety; the use of operative cholangiography (whether routine, selective or never) remains controversial, but there is insufficient evidence to support the view that routine cholangiography will prevent major bile duct injury. Although laparoscopic choledochotomy is being increasingly reported, a policy of endoscopic treatment of CBD stones before and/or after surgery remains the norm. The operative mortality rate at <0·2 per cent is appreciably lower than after conventional cholecystectomy. The hospital cost also appears to be less than that of the open procedure and the patient can expect to return to work within 1–2 weeks, compared with 6–8 weeks following conventional cholecystectomy.

Laparoscopic cholecystectomy is undoubtedly here to stay and, despite the absence of a controlled trial, has become rapidly established into surgical practice. The major reported problem of common duct injury can be reduced by good technique and appropriate training. Several lessons learned from this new procedure should be applied to other new laparoscopic techniques. The value of training to learn safe technique and the value of honest and comprehensive audit are two of the more important messages that surgeons should heed as the laparoscopic revolution progresses.

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Addendum

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A2. Mouret G. From the first laparoscopic cholecystectomy to the frontiers of laparoscopic surgery: the future perspectives. *Dig Surg* 1991; **8**: 124–5.
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Radiological investigation in acute diverticulitis

Optimal management of acute sigmoid diverticulitis depends on evaluation of the severity of the inflammatory process, in which radiological investigation is a useful but probably underutilized adjunct to clinical assessment. Plain abdominal radiography shows abnormalities in 30–50 per cent of patients but these tend to be non-specific and more accurate information is obtainable from a contrast enema. Although the quality of images produced by a water-soluble contrast agent is inferior to that with barium, the former is less hazardous in the presence of perforation and provides sufficient information to permit rational management decisions to be made. Ultrasonography and computed tomography (CT) are particularly useful in visualizing abscesses. They may be helpful in following the progression or resolution of suppuration and in guiding percutaneous aspiration when appropriate. Despite early reports to the contrary, CT is no more specific than a contrast enema in the diagnosis of acute diverticulitis. Radionuclide scans have little role in the routine assessment of acute diverticulitis and magnetic resonance imaging has not been adequately evaluated. Water-soluble contrast enema is safe, widely available and probably the most useful early supplementary investigation.

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Diverticular disease of the colon affects up to two-thirds of the population over the age of 70 years[1] and symptomatic complications occur in 10–30 per cent of patients[2–4]. Acute inflammation secondary to sigmoid diverticula is, therefore, a relatively common reason for emergency hospital referral. Although only 15–30 per cent of patients admitted with 'acute diverticulitis' require operation[5,6], mortality and morbidity rates can be high if emergency surgery is necessary[7,8]. The outcome of an acute infective episode is multifactorial, depending on the severity of sepsis and peritoneal contamination, age, presence of coincidental pathology and the impact of treatment.

Stratification of the pathology of acute diverticulitis[8] (*Table 1*) not only permits assessment of the published results of treatment but also helps clinical decision making by emphasizing the spectrum of disease encountered. There has been a trend towards conservative management of acute diverticulitis[9,10] based largely on clinical criteria, such that early radiological assessment has not been widely used, particularly in the UK. Such reluctance to perform urgent radiological investigations, if based on concern over safety and uncertainty regarding their impact on management, may be inappropriate.

The clinical diagnosis and assessment of acute diverticulitis can be difficult[4,11,12], but early investigation with confirmation of the diagnosis is fundamental in the trend towards more conservative management[8,10,13]. Early investigation is useful in confirming the diagnosis, thus avoiding inappropriate therapy, and in assessing the site and severity of the inflammatory process, which may identify patients less likely to respond to conservative treatment. This review examines the literature on the radiological investigation of acute diverticulitis to determine the utility and safety of such investigation in clinical practice.

Plain radiography

An erect chest radiograph, together with erect and supine films of the abdomen, is usually obtained in patients with significant abdominal pain. Abnormalities such as pneumoperitoneum (*Figure 1*), ileus, complete or partial bowel obstruction, or a soft tissue mass (*Figure 2*) are found in 30–50 per cent of patients with acute diverticulitis[13,14] but are not specific to this condition. Erect chest radiography is valuable for two reasons:

Table 1 *Operative pathology of acute diverticulitis*

- Acute inflammation without pus formation
  - Acute phlegmonous diverticulitis
- Pus present
  - Localized
    - Localized peritonitis
    - Abscess
  - Generalized
    - Purulent
    - Faecal

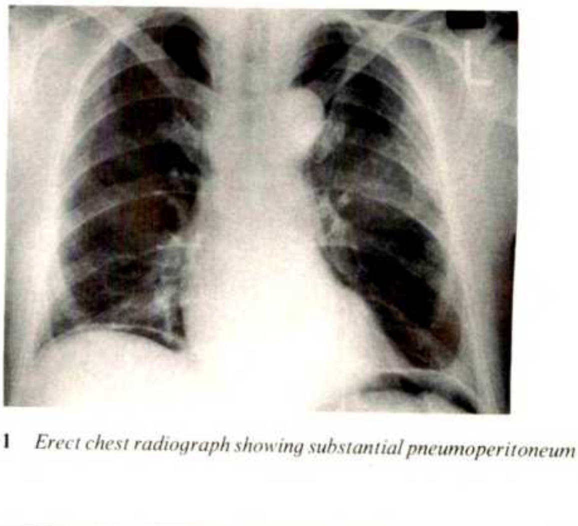

Figure 1 *Erect chest radiograph showing substantial pneumoperitoneum*

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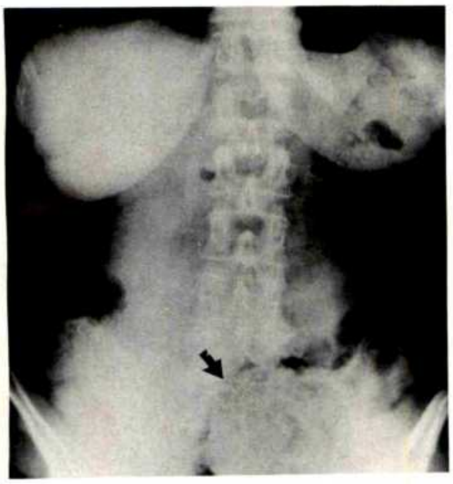

Figure 2 *Erect abdominal radiograph showing a large soft tissue mass (arrow) in the left lower quadrant*

first, coincidental cardiorespiratory pathology is present in 27–33 per cent[15,16] of patients presenting with an acute abdomen; second, the erect chest radiograph is the most sensitive means of identifying pneumoperitoneum[17]. The latter is found in only 3–12 per cent[11,13,14] of patients with acute diverticulitis. If an erect film is impractical, left lateral decubitus radiography may detect free peritoneal air[17–19]. Signs of pneumoperitoneum on supine abdominal films include: (1) Rigler's sign where both sides of the bowel wall are outlined by gas[20]; (2) the falciform ligament appears as a linear density in the right upper quadrant[21]; (3) the lateral umbilical ligaments appear as an inverted V shape over the sacrum[19]; and (4) triangular collections of air.

The value of the erect abdominal radiograph in the management of acute abdominal pain has been questioned[16,22–24] but it may demonstrate an otherwise inapparent intra-abdominal abscess[16] and still retains a place in management.

Contrast studies

Water-soluble contrast enema

This study is performed on unprepared bowel and no air contrast is used[11]. The radiological characteristics of acute diverticulitis on water-soluble contrast enema have been classified[11,24] as:

1. Diverticulosis with or without spasm.
2. 'Peridiverticulitis' – marked sigmoid irregularity with long strictures or obstruction.
3. Extravasation of contrast (*Figure 3*).

The absence of diverticula or other abnormality requires urgent review of the diagnosis[25]. In a recent prospective study[26] of 53 patients with a clinical diagnosis of diverticulitis who had an early water-soluble contrast enema, only 49 per cent had acute colonic diverticulitis as a final diagnosis. Kourtesis *et al.*[13] observed a correlation between radiological features and the need for emergency surgery. Three of 30 patients with diverticulosis or spasm required operation, compared with 13 of 16 with peridiverticulitis or extravasation. Water-soluble contrast enema can be performed safely within a few hours of admission[11,24,27]. Wexner and Thomas[27] found that its early use was associated with a lower rate of misdiagnosis and a shorter hospital stay in comparison with delayed barium enema or no contrast enema. Water-soluble enemas are hyperosmolar and the resulting fluid shift into the bowel may compound oligaemia if fluid resuscitation is suboptimal. In practice, however, they do not exert a detrimental effect and are a simple and safe preliminary contrast investigation in patients with suspected diverticulitis.

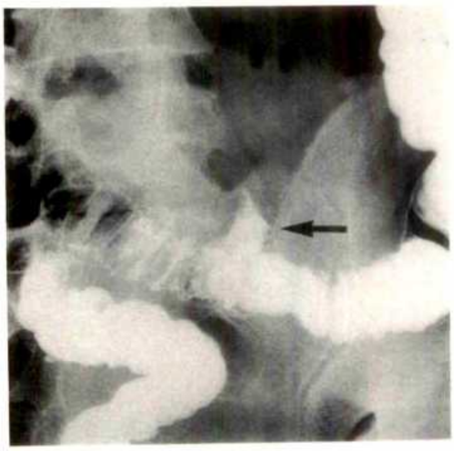

Figure 3 *Water-soluble contrast enema performed on day of admission showing extravasation of contrast in an area of sigmoid diverticular disease (arrow)*

Barium enema

Although barium enema provides better contrast and mucosal detail than a water-soluble study, it has disadvantages in the early assessment of diverticulitis. Barium enema is contraindicated in patients with pneumoperitoneum, who are haemodynamically unstable, or who have a history of (deep) rectal biopsy within 7 days previously[28,29]. For an emergency barium study, bowel preparation is not required; a gentle single contrast study should be performed by an experienced radiologist[28,30,31]. Although it is recommended that the examination be terminated once significant radiological changes have been demonstrated[31], the possibility of coincidental proximal pathology must be borne in mind and further investigation by double-contrast study or colonoscopy may be required. As in water-soluble contrast enema studies, the radiological appearances may be those of diverticula alone or of associated inflammatory features: pericolic mass, abscess, obstruction or extravasation of barium[2]. The demonstration of diverticula does not necessarily equate with complicated diverticulitis and, equally, a grossly inflamed colon may have no recognizable signs of inflammatory change on barium enema[32]. Nicholas *et al.*[32] reviewed preoperative barium enema findings in 76 patients with gross inflammatory masses found at operation for diverticulitis. In 14 per cent no radiological signs of diverticulitis (i.e. external pressure, spasm, extravasation) were recorded, but considerable variation does exist between radiologists in the interpretation of the radiographic features of diverticular disease[33]. Although these studies[32,33] were performed before double-contrast enema became routine, they remain relevant because only single-contrast studies are appropriate in acute diverticulitis.

The potential changes are not pathognomonic of diverticular inflammation; they may occur in Crohn's disease and carcinoma. Ferrucci *et al.*[34] described 'double tracking' of contrast in the inflamed bowel wall, with barium extending along a longitudinal track in the submucosa or subserosa parallel to the lumen. Luminal narrowing of the bowel because of inflammation is common, and differentiation from carcinoma is a problem in 15–25 per cent[30,35] of patients with a provisional diagnosis of diverticulitis. Radiological signs favouring the diagnosis of diverticulitis rather than carcinoma include the absence of mucosal destruction, tapered rather than shouldered margins of the lesion, and the involvement of >6 cm of bowel[36]. In inflammatory disease severe spasm may be reversed by the intravenous administration of a spasmolytic agent such as glucagon[30,36,37]. In a study of 73 barium enemas in patients with diverticular disease and/or colonic carcinoma, the overall error rate compared with final histological finding was 23 per cent[35]. Differentiation from Crohn's disease may be difficult because both conditions produce fistula and abscess[36], although Crohn's disease is characterized by oedematous ulcerated mucosa. An extraluminal mass compressing or displacing the bowel is the most common radiological finding in diverticulitis (65 per cent in one series[32]) and smaller masses may result in a marginal filling defect; however, colonic carcinoma, serosal metastases and endometriosis create similar appearances. The most reliable radiological sign of inflammation in diverticular disease is extraluminal barium indicating perforation of a diverticulum[30–32,36,38]. Free perforation into the peritoneal cavity is occasionally seen, but extraluminal barium is more likely to outline an abscess cavity or fistula track and be detectable only on postevacuation radiography[30,31,36].

Choice of contrast agent

Despite the extensive literature on the use of contrast enema in acute diverticulitis, there is no consensus on either the best contrast agent or the optimal timing of the examination. Although many authors advocate barium as the contrast medium of choice, provided pneumoperitoneum has been excluded[28,30,31,36], others advise against any enema examination 'during the acute phase'[39] or for up to 2 weeks after[40] an episode of diverticulitis. Clinically it is not possible to exclude a small perforation and, since the consequences of faecal–barium peritonitis are potentially serious[41,42], the choice of contrast agent is relevant. An additional disadvantage of barium is its persistence in the colon, which causes interference with subsequent investigation and with cleaning of the bowel at operation.

When pneumoperitoneum is present or suspected, therefore, a water-soluble contrast medium is mandatory[25,36,43,44] and there is a strong case for the routine use of such agents in acute diverticulitis[11,24,27]. Although subtle radiographic changes may be missed in water-soluble contrast studies[2], owing to the inferior quality of the contrast and of mucosal coating, in practice the demonstration of luminal narrowing, extravasation and diverticula is usually sufficient to permit rational management decisions to be made. Double-contrast barium enema and/or colonoscopy should be performed after recovery from an acute episode[30,36] to provide a more complete examination of the bowel or to resolve diagnostic doubt arising from the difficulty in demonstrating coincidental carcinoma or polyps in diverticular disease[45].

Ultrasonography

The role of ultrasonography in the initial assessment of acute diverticulitis has not been extensively documented. Parulekar[46] described sonographic findings in 16 patients with diverticulitis in 1985. Characteristic thickening of the wall (up to 17 mm in thickness and averaging 7 cm in length) was seen in segments of colon, producing a 'pseudokidney' sign[47]. Sonographic signs of abscess formation were found in seven of the 16 patients, although barium enema revealed definite evidence of abscess with extravasation of contrast in only two. An extrinsic mass effect was noted in a further three enemas. Individual diverticula may be demonstrable on ultrasonography, which Parulekar advocated as the initial imaging investigation, arguing that a positive result might avoid an early contrast examination in an ill patient. Serial scans could be used to monitor response to conservative management because a progressive decrease in wall thickness of abnormal segments of colon is seen during resolution of acute diverticulitis.

Two recent studies also support the use of ultrasonography as an initial investigation[48,49]. In a prospective series[48] of 123 patients with acute abdominal pain, 52 of whom were eventually diagnosed as having acute diverticulitis, ultrasonography had a sensitivity of 85 per cent and specificity of 80 per cent, compared with the final clinical diagnosis based on contrast study or surgical exploration. Diagnostic criteria included thickening of the bowel wall of >4 mm over a segment of bowel ≥ 5 cm long in the left side of the abdomen, and demonstration of diverticula or abscess cavities next to the bowel. Wilson[49] studied 70 patients with clinical features of acute diverticulitis; 54 had sonographic findings consistent with this diagnosis. Some 46 patients had a final diagnosis of acute diverticulitis, six had other causes of colonic inflammation and two had diverticular disease without active inflammation, at subsequent laparotomy.

A potential advantage of ultrasonography is that it may play both a diagnostic and a therapeutic role in the management of abscess, since it allows guided percutaneous drainage[50]. A disadvantage is that bowel wall thickening, the most common sonographic abnormality in acute diverticulitis, is a non-specific finding that also occurs in Crohn's disease, carcinoma, lymphoma and metastasis. The detection of diverticula makes the diagnosis of diverticulitis more likely, but the incidence of such detection on ultrasonography varies from 5 to 72 per cent[48,49]. Such differences illustrate the operator variability inherent in ultrasonography compared with contrast studies or computed tomography (CT), in which subjective interpretation is less problematic. No comparative studies of ultrasonography with either contrast studies or CT have been published.

Computed tomography

The value of CT in the demonstration of intra-abdominal abscess was recognized at an early stage[51] although its potential in the assessment of diverticulitis was not reported[52] until 1982. CT was considered a useful adjunct in the investigation of gastrointestinal disease, particularly if a mesenteric or extramural process was suspected[53]. In 1982, Gore and Goldberg[52] reported that the method supplemented a barium enema diagnosis of diverticulitis by defining the extent of pericolonic involvement and demonstrating thickening of the bowel wall, narrowing of the lumen and inflammatory change in the surrounding structures (*Figure 4*) in addition to abscess formation. Lieberman and Haaga[54] documented the features of acute diverticulitis on CT: bowel wall thickening, increased soft tissue density within the pericolic fat secondary to inflammation, and large soft tissue masses representing either phlegmon or abscess. These authors suggested that CT might influence management; patients in their series with large soft tissue masses were likely to require surgery.

Hulnick *et al.*[55] carried out the first large retrospective study of the use of CT in diverticulitis, describing the findings (*Table 2*), evaluating the utility of the method, and comparing it with contrast enema. The latter underestimated the extent of disease in 41 per cent of patients compared with CT, which was more sensitive in demonstrating the presence and extent of inflammation and abscess. These authors concluded that CT should become the investigation of first choice in patients with diverticulitis, but emphasized the value of subsequent contrast

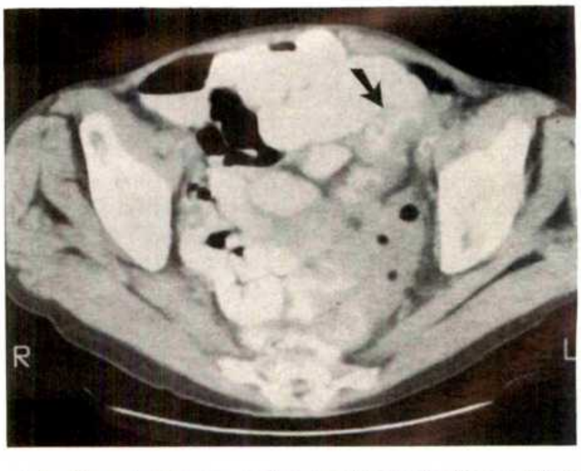

Figure 4 *Computed tomogram showing thickened colonic wall (arrow) and narrowed lumen resulting from diverticulitis*

enema for better evaluation of mucosal detail to exclude carcinoma.

A number of studies have evaluated CT and compared it with barium enema[14,56–63]. Only those of Pillari *et al.*[58] and Cho and colleagues[63] were prospective and the remainder have variable diagnostic criteria for acute diverticulitis, with only a small proportion of patients undergoing both CT and barium enema[14,56,60]. While CT may appear less invasive than contrast enema, rectal contrast is often used[58,63] and so this advantage is lost, but CT does provide better definition of the extent and severity of the pericolic process. Barium enema allows evaluation of mucosal detail but is less accurate for pericolic abscess and extraluminal changes. In one study, in which all patients underwent both CT and barium enema[62], 28 of 31 CT scans and 29 of 31 barium enemas were abnormal; 20 scans and 19 enemas were diagnostic, CT being thought particularly useful in demonstrating the cause of retrograde obstruction on barium enema.

Early enthusiasm for CT has been tempered by increasing experience; inaccuracies, usually suggestive of tumour, occurred in 10 per cent of 150 patients with acute diverticulitis in one study[61]. Difficulties arose when inflammatory changes were either so marked as to mimic carcinoma or were too trivial with insufficient inflammatory response to be demonstrable. Barium enema proved helpful in the majority of equivocal cases. Early information provided by CT may influence management, and Neff and van Sonnenberg[64] proposed a CT staging system (*Table 3*) based on the surgical classification of Hinchey *et al.*[65] with a suggested plan of management. We would not concur with their recommendations for treatment, which are unnecessarily interventional. In our experience, careful conservative treatment is effective in many cases, even when florid perforation and abscess is demonstrated[66] (*Figures 2, 5* and *6*), and we would intervene, either with operation or percutaneous drainage, only if more conservative therapy had failed.

In the acute phase of diverticulitis, CT is indicated where management remains in doubt despite the more readily obtainable contrast enema. Many authors emphasize the complementary role of the two techniques and advise subsequent barium enema to exclude carcinoma in patients who have not undergone surgery[61,63,67–69].

Table 2 *Computed tomographic criteria for diagnosis of acute diverticulitis*[55]

Feature	Frequency (%)
Inflammation of pericolic fat	98
Diverticula	84
Thickened colonic wall (>4 mm)	70
Pericolic abscess	35
Peritonitis	16
Fistula formation	14
Extrapelvic abscess	12
Colonic obstruction	12
Intramural sinus tracks	9
Ureteric obstruction	7

Table 3 *Computed tomographic staging of sigmoid diverticulitis*[64]

Stage	Definition
0	Inflammation confined to colonic wall
I	Small abscess or phlegmon 3-cm abscess confined to mesentery
II	Abscess extending out of mesentery but confined by pelvic structures 5–15-cm 'pelvic abscesses'
III	Spread out of pelvis
IV	Generalized peritonitis Tomographic findings same as stage III but clinically acute peritonitis with life-threatening sepsis

Nuclear imaging

Radioisotope scanning is limited to the localization of a septic focus when the source of infection is not apparent on routine clinical, radiological or ultrasonographic examination[70]. ^{67}Ga citrate localizes in polymorphs and consequently in inflammatory foci, although serial scanning over up to 72 h is necessary[71]. The isotope is, however, also taken up by tumours and 25 per cent of the dose is excreted in the gut, limiting its use in intra-abdominal diagnosis[71]. ^{111}In has a shorter half-life of 5–8 h and a scan using ^{111}In-labelled leucocytes can be completed in 24 h; unfortunately the labelling method is time consuming and expensive. Indium is not excreted in the gut but does accumulate in the spleen[72]. Neither ^{67}Ga nor ^{111}In scans can distinguish between inflammatory mass and abscess[70]. Leucocytes labelled with ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) have been used to investigate patients with diverticulitis; this technetium-carrying label makes the investigation easier and relatively cheap. In a study of 18 patients, Lindahl *et al.*[73] showed accumulation of isotope in 13 within 30 min of injection. However, such 'hot spots' are non-specific and occur with any inflammation, be it abscess, inflammatory bowel disease or pyosalpinx. Supplementary single-photon emission CT may provide more accurate anatomical localization[73]. Although imaging with ^{99m}Tc-HMPAO-labelled leucocytes is superior to that with ^{111}In-

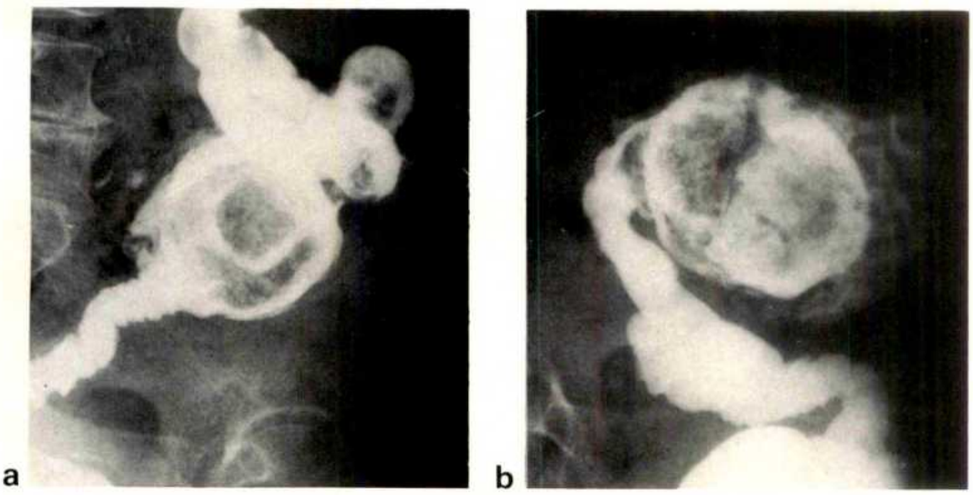

Figure 5 **a** *Right oblique and* **b** *anteroposterior water-soluble contrast enema demonstrating an abscess cavity.* (*Same patient as in* Figure 2)

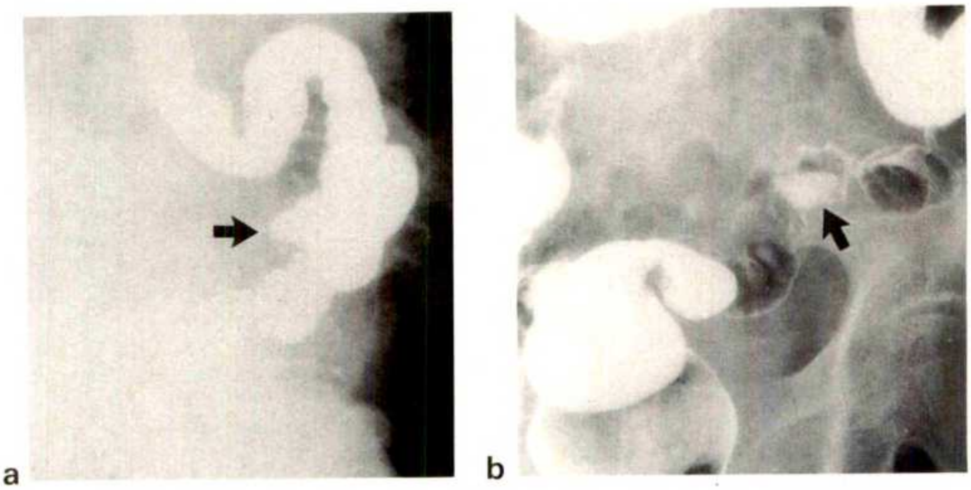

Figure 6 **a** *Right oblique and* **b** *anteroposterior barium enema 6 weeks later showing resolution of abscess (arrow). (Same patient as in* Figure 5)

labelled cells, it is of no practical value in management because the intra-abdominal source of sepsis is invariably obvious, and more useful information can be derived from contrast studies, CT or ultrasonography[74].

Magnetic resonance imaging

The potential of magnetic resonance imaging (MRI) for investigation of oesophageal and rectal abnormalities is becoming established[75]. In other areas of the gastrointestinal tract its applicability is limited by motion artefacts induced by cardiac, respiratory and peristaltic movement, reduced spatial resolution compared with CT, and metallic implants[69]. MRI can detect bowel thickening and, while a role in investigating diverticulitis has been proposed[75], the method cannot yet be recommended although reductions in scan times and developments in intraluminal contrast will doubtless extend its applicability.

Conclusions

Successful management of acute diverticulitis depends on resolution of peritoneal sepsis. Conventional wisdom dictates that clinical symptoms of diffuse peritonitis are indications for laparotomy, although mild and localized abdominal signs are generally managed conservatively. The boundary between appropriate conservative management and operative intervention is ill defined. A conservative policy for the management of acute diverticulitis appears effective[66] but requires early confirmation of the diagnosis to avoid inappropriate treatment of conditions for which urgent operation is essential.

Under these circumstances early water-soluble contrast enema is safe, even in the presence of pneumoperitoneum, and should be routine. If the clinical diagnosis of diverticulitis is refuted, management must be reconsidered. Patients more likely to require emergency intervention, such as those with extravasation into the peritoneal cavity or abscess, can be identified. CT is best for visualizing abscess and pericolonic inflammation, and may guide percutaneous drainage if resolution seems unlikely or does not occur with antibiotic therapy. The limited access to CT and MRI remains a restriction on their use in many centres and the lack of mucosal detail is a clinical disadvantage. Ultrasonography is more widely available and is useful, particularly in the hands of an experienced operator, in identifying lesions, guiding aspiration and in the serial study of abscess. Successful resolution of an acute inflammatory episode, however, should be followed in the majority of patients with a double-contrast barium enema and/or colonoscopy both to confirm the diagnosis and to exclude colonic cancer, which coexists in approximately 15 per cent of patients. Finally, while management decisions should be influenced by the results of radiological investigations (otherwise it is pointless to request them), the decision to intervene depends on the patient's clinical condition and response to treatment, rather than radiological appearance.

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Gene transfer therapy in cancer

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Gene transfer techniques have now achieved clinical realization in the wake of recent advances in recombinant DNA technology, together with increased understanding of the molecular biology and immunology of cancer. These novel treatments, and their applications and limitations merit intensive study.

The current therapeutic techniques available for the treatment of patients with cancer are surgery, radiotherapy and chemotherapy. However, conventional chemotherapy has largely failed to have a significant impact on survival in the treatment of most solid tumours[1]. Surgery continues to be the most effective treatment for primary tumours and can be curative. A search has been conducted for effective and non-toxic adjuvant therapy for patients with minimal residual disease after operation.

Several observations suggest that a host immune response is often mounted in an attempt to reject the tumour. First, many solid tumours contain an immunological infiltrate, which in some is considered to be a good prognostic indicator[2–4]. Second, spontaneous regression of advanced disease sometimes occurs in immunogenic tumours such as melanoma and renal cell carcinoma[5]. Finally, immunosuppressed patients have an increased incidence of malignancy, although lymphoid tumours rather than carcinoma predominate in this susceptibility[6–8]. The therapeutic extrapolation of these findings has culminated, in the past decade, in the emergence of biological or immunological therapy for cancer[9–12]. Biological treatment represents a conceptual leap as the therapy does not itself have a direct tumoricidal effect but acts by stimulating host immune mechanisms to mediate tumour regression.

Several immunological prerequisites must be met before an effective immune response can be mounted against a tumour. There must be antigenic determinants that are expressed selectively, if not exclusively, on tumour as opposed to normal cells[13]. These tumour antigens must be presented to the immune system in the context of the major histocompatibility complex (MHC) antigens class I or II so that peripheral T cells can recognize them as foreign[14]. This has been the basis of many disappointing attempts at producing cancer vaccines in clinical studies[15]. In addition, the antigens must stimulate both helper T cells and cytotoxic T lymphocytes to ensure tumour destruction[16,17].

The cornerstone of biological therapy in the treatment of solid tumours has, until recently, involved the systemic administration of high-dose cytokines such as interleukin (IL) 2 and interferon (IFN)[18]. The rationale of this approach was initially either to generate direct killing of tumour cells (in the case of IFN) or provide activation of tumour-specific cytotoxic T lymphocytes by IL-2, thereby compensating for any defects in the helper T cell arm of the immune system that might be preventing tumour clearance *in vivo*. Although sporadically effective, these treatments are associated with severe side-effects and even fatalities[19]. The systemic levels of cytokines causing toxicity are well below the serum concentrations that are effective against tumours in animal models[12]. However, if high levels of these agents could be produced locally among tumour cells, they may effect tumour regression without the associated toxicity of systemic administration[20]. This possibility has formed part of the rationale for the initiation of clinical gene transfer studies in cancer. However, advances in understanding the molecular basis of the immunological response to cell-surface cancer antigens have also contributed to the emergence of therapeutic gene transfer for vaccination against some solid tumours[21]. Immunotherapy seeks to harness two unique characteristics of the immune system, namely antigenic specificity and response amplification, in selectively activating a strong immune response to induce tumour cell lysis.

Additionally, examination of tumour material has revealed alterations in several genes that are responsible for cell growth and proliferation. The molecular basis of cancer is now known to involve the activation of dominant oncogenes[22] and the inactivation of recessive tumour suppressor genes[23]. These genetic events can themselves be viewed as potential targets for cancer therapy.

In this paper, the current concepts of clinical gene transfer therapy in the treatment of solid tumours are reviewed and their potential or actual clinical applications discussed. The limitations, ethical considerations and future directions of this form of therapy are also addressed.

Therapeutic gene transfer

Gene transfer involves the insertion of novel genetic material into the genome of a target cell to produce a new cellular phenotype. Therapeutic gene transfer has evolved from the development of techniques for inserting and expressing genes in eukaryotic cells[24] and from advances in the understanding of the regulation of gene expression[25].

An essential prerequisite of any such technique is the efficient and stable delivery of the transferred DNA into the target cell. Retroviral expression vectors fulfil these requirements; they are retroviruses in which the viral genes have been replaced with therapeutic genes[26–28]. Viruses are naturally occurring genetic vectors and thus lend themselves to gene transfer. Retroviral vectors can efficiently carry foreign genes into the cell such that they become integrated and expressed in a predictable and, usually, very stable manner[27]. The precise site of integration of the vector in the host cell genome is, however, largely random. This is a source of concern for the use of retroviral vectors in gene transfer protocols, because of the small, but finite, risk of integration into a critical cellular gene. Retroviruses are also limited largely to the infection of replicating cells[29]. The retroviral vector is incapable of making any viral protein necessary for replication. Proteins required for initial infection of target cells are provided by retrovirus-packaging cells[28]. Introduction of the retroviral vector into the

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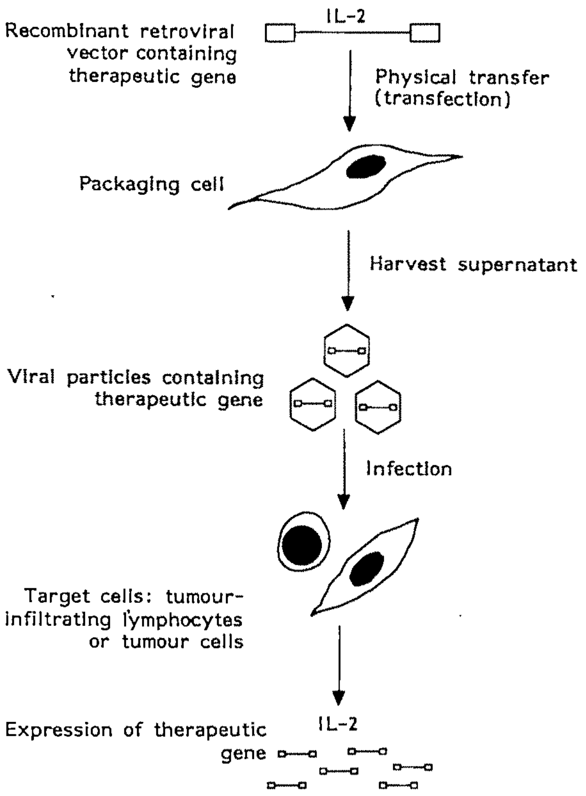
Recombinant retroviral vector containing therapeutic gene
IL-2
Physical transfer (transfection)
Packaging cell
Harvest supernatant
Viral particles containing therapeutic gene
Infection
Target cells: tumour-infiltrating lymphocytes or tumour cells
Expression of therapeutic gene
IL-2

Figure 1 *Retrovirus-mediated gene transfer, exemplified for interleukin (IL) 2*

packaging cell results in the production of viral particles that can be used to infect the target cells but, importantly, no virus spread occurs after this initial infection[28,30]. This process is summarized in *Figure 1*.

The major disadvantage of retrovirus-mediated gene transfer is the potential for the production of replication-competent (helper) virus. This can occur by recombination between retroviral vector DNA sequences and viral coding sequences in the packaging cells[28]. However, this risk has been greatly reduced by careful design of the packaging cell lines[30], and in human trials thus far there is no evidence to indicate that patients have been exposed to replication-competent retroviruses[31,32].

Retrovirus-mediated delivery is currently the method of choice in clinical gene transfer studies[31]. However, other techniques are under investigation using as vectors other types of virus that can infect non-replicating cells such as central nervous system tissue[33]. There are also physical methods by which genes can be directly delivered to cells either *in vitro* or *in vivo*, including coating of DNA in liposomes or a precipitate of calcium phosphate, both of which increase the efficiency with which DNA traverses the cell membrane. The efficiency of such methods is, however, significantly lower than that which can be achieved using viral-based techniques.

Protocols of immunotherapy

A tumour deposit consists of different cellular components. From a therapeutic perspective, these can be broadly divided into malignant cells and immunological cells that are frequently present in tumour infiltrate (*Figure 2*). It has been assumed that the presence of such an infiltrate is indicative of an

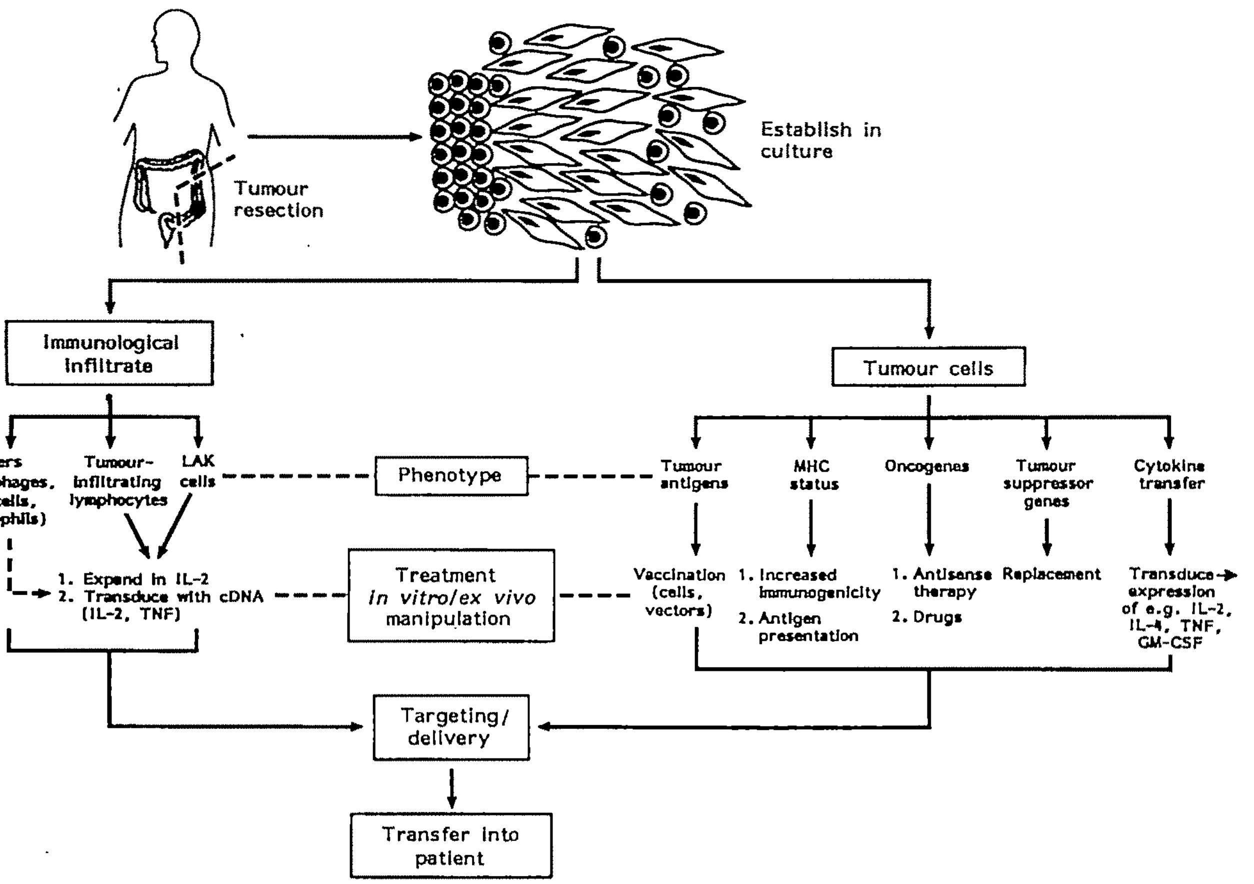

Figure 2 *Potential manipulations of immunological infiltrate or tumour cells, from tumour resection to transfer of altered cells into the patient. MHC, major histocompatibility complex; NK, natural killer; LAK, lymphokine-activated killer; IL, interleukin; TNF, tumour necrosis factor; GM–CSF, granulocyte–macrophage colony-stimulating factor*

antitumour response[2–4]. Moreover, the infiltrating cells presumably also have a natural tumour-localizing specificity, a property that can be exploited therapeutically[34,35].

The patient's ability to mount an effective response to the tumour can be enhanced by increasing the antitumour potency of the infiltrating cells and/or by manipulating the tumour cells to become more immunogenic. Advances in molecular technology have resulted in characterization of some of the genes of the putative tumour antigens themselves[21], of accessory molecules involved in their immunological presentation[36] and of immunomodulatory cytokines[37]. Additionally, novel genetic vehicles and vectors now exist with which to present these components to the immune system[28].

Tumour-infiltrating immune cells

The discovery of the T cell growth factor IL-2 led to the ability to expand T cells *in vitro* and *in vivo*. As a result, clinical trials of IL-2 for cancer therapy were rapidly established[38,39]. Systemic administration of IL-2 led in some cases to a dense lymphoid infiltration of the tumour and, in some instances, tumour regression was observed[40–42].

Such observations show that T cells play a pivotal role in the immune response to cancer. The next step[34,43] was to use recombinant IL-2 to expand populations of immune cells recovered from resected tumours followed by adoptive transfer of these populations back into the patient together with high doses of systemic IL-2. These cells consist of tumour-infiltrating lymphocytes and lymphokine-activated killer (LAK) cells. Subsequent studies revealed that tumour-infiltrating lymphocytes are 50–100 times more effective in destroying tumour than are LAK cells[35,44]. Such regimens have been associated with spectacular tumour regression in some patients with advanced metastatic disease from melanoma, but at the expense of severe side-effects[32,34,45].

The cloning of many cytokine genes has made the prospect of manipulating immune effector cells to express high levels of potentially therapeutic cytokines or growth regulators a clinical reality. These cells can be administered back to the patient, where they are expected to secrete these proteins in the tumour deposits in locally high, but systemically negligible, concentrations. Tumour-infiltrating lymphocytes target tumour tissue with high efficiency as this is the basis of their operational definition[32,44]. Furthermore, the specificity of such immune cells for their tumour targets makes tumour-infiltrating lymphocytes attractive candidates for treating clinically undetectable metastases[34]. Response rates of 40 per cent have been reported in patients with advanced melanoma treated with tumour-infiltrating lymphocytes but long-term survival rates remain disappointing[34].

In an initial study of the use of gene-modified T cells, tumour-infiltrating lymphocytes were recovered from melanomas in six patients and genetically marked by infection with a recombinant retroviral vector encoding a reporter gene[32]. (Reporter genes serve no therapeutic purpose and are inserted into a cell simply to mark it biologically, usually with a gene for drug resistance. This allows an investigator to follow the fate of the cell in the body.) Reinfusion of these marked tumour-infiltrating lymphocytes back into patients revealed that they could be detected in tumour deposits and the peripheral circulation for several weeks following transfer. The presence of the marker gene had no effect on the efficacy of the tumour-infiltrating lymphocytes, which induced a response in half of the patients, but importantly demonstrated their innate tumour specificity and also the lack of harmful side-effects associated with treatment by cells modified by recombinant retroviral vectors[32]. Use of adoptively transferred tumour-infiltrating lymphocytes as vehicles for gene therapy is under way, and such lymphocytes from patients with melanoma have been infected with a retroviral vector expressing tumour necrosis factor (TNF)[46,47]. It is too early to assess this trial, but initial results are awaited. Success in this study will promote the use of other recombinant cytokine genes (e.g. IL-2, IL-4) for transduction of tumour-infiltrating lymphocytes.

There is variation in both the density and composition of the tumour infiltrate between different tumours of the same histopathological type. Thus both helper T cells and cytotoxic T lymphocytes, as well as natural killer cells, LAK cells, eosinophils, macrophages and neutrophils, are present in varying proportions[48–50]. Some of these immune cells mediate non-MHC restricted lysis of tumour cells and may prove to be of as much value in immunotherapy as tumour-infiltrating lymphocytes, which have been the principal cell type studied so far. Indeed, the nature of the infiltrate may predict appropriate manipulation of the tumour cells required to recruit greater numbers of relevant immune cells.

Targeting of tumour cell

The alternative to manipulating the immune infiltrating cells is to study the malignant cells themselves and define tumour-specific characteristics that can be used to induce cell death directly or promote tumour cell rejection (cancer vaccination) (*Figure 2*).

Tumour antigens and vaccination. To date, candidate cancer vaccines have used autologous (MHC matched) or allogeneic (MHC mismatched) tumour cells, or tumour cell-derived preparations, in conjunction with an adjuvant (e.g. bacille Calmette–Guérin vaccine) to enhance antitumour immunity[51,52]. In the absence of purified tumour antigens of known efficacy, tumour cells have been the best way to ensure that any tumour-specific antigens are presented to the immune system. The heterogeneity of tumour phenotypes, even between different tumour deposits in the same patient, necessitates the presentation of as large a variety of antigens as possible to produce a vaccine of even moderate efficacy. The synergy produced by combinations of tumour-associated antigens on tumour cell preparations is crucial to generate strong cell-mediated rejection immunity against the tumour. Apart from isolated reports of encouraging responses[53], the use of whole tumour cells and preparations derived from them as vaccines has yielded disappointing results[51].

Ideally, a cancer vaccine should possess a broad antigenic complexity, as well as a high degree of specificity of antigenic stimulation. However, whole cell preparations contain a plethora of irrelevant antigens, which induce redundant immune responses that can hinder tumour-specific activity. Nevertheless, it is now possible to clone, re-express and assess potentially clinically relevant tumour antigens to determine their role in tumour cell rejection, leading to the isolation of elements that produce the greatest therapeutic benefit by inclusion into 'designed' vaccines[13,21]. So far, melanoma is the only human malignancy in which a tumour antigen has been defined at a molecular level that is recognized by autologous cytotoxic T lymphocytes from the patient. Immunological techniques are now able to define antigens that are recognized *in vitro* by cytotoxic T lymphocytes derived from a patient with a tumour. Using gene transfection techniques and a cytotoxic T lymphocyte-based selection assay, Van der Bruggen and colleagues[54] cloned a gene for a melanoma antigen called MZ2-E. The MZ2-E antigen is expressed on melanoma and several other histological types of tumour but not on a panel of normal tissues. As MZ2-E has been cloned using cytotoxic T lymphocytes from patients with melanoma, it is expected that this tumour-specific antigen will have relevance in *in vivo* antitumour immunity. Immunological presentation of MZ2-E was also found to be human leucocyte antigen (HLA) A restricted[54] (that is, only one type of MHC molecule will present the antigen to the immune system). Therefore, cancer vaccines must also take into consideration the MHC genotype status of the patient. It is hoped that similar approaches will be applied to the cloning of other tumour-specific antigens for other carcinomas. Tumour antigens need not necessarily be proteins. Indeed, some carbohydrate moieties expressed in glycoproteins or mucins on epithelial cancer cells are known to be immunogenic in man, and a vaccine expressing a sialomucin antigen is undergoing trials in patients with colorectal cancer[55].

Mutated oncogene products and tumour suppressor genes are also theoretical candidates as rejection antigens in a range of tumours[56]. The immunogenicity of such mutated proteins has not yet been demonstrated in human cancers, but the predominance of oncogene activation might make these proteins immunogenic targets for vaccines.

Major histocompatibility complex antigens. Experimental evidence has demonstrated that a decrease in the expression of cell-surface MHC class I antigens increases the tumorigenic potential of various transformed cells. For instance, the tumorigenicity of several cancer cell lines in mice can be partially abrogated by transfection of a single MHC class I gene into the tumour cells[57,58]. Importantly, transfected class I-positive tumour cells were able to sensitize a syngeneic mouse host to reject an otherwise tumorigenic dose of class I-negative parental tumour. This is an absolute prerequisite if MHC replacement is to offer a realistic vaccine strategy, as delivery of an appropriate MHC gene to every tumour cell in the body is not possible. These results are consistent with the known role of MHC class I in the presentation of foreign or tumour-associated antigens on the tumour cell surface to cytotoxic T lymphocytes[59]. Therefore, decreased expression of MHC molecules, class I in particular, might allow transformed cells to escape immune detection and allow tumour progression[60].

Clinical observations also suggest that loss of MHC may enhance tumorigenicity. The HLA class I antigens are downregulated in about 10 per cent of primary melanoma lesions and in 30 per cent of metastatic nodules[61]. Moreover, there is a significant association between low levels of class I antigens and a poor outcome in melanoma[62]. Losses of HLA have also been reported in a variety of other solid tumours[63]. It is possible, therefore, that the delivery of MHC molecules to tumour cells, and the expression of the corresponding antigens, may increase their recognition by the immune system and augment their rejection. Indeed, this strategy has formed the therapeutic basis of the initiation of a clinical study using liposome-mediated transfer of an HLA-B27 molecule directly into the tumour deposits of patients with advanced melanoma[64].

Tumour cells engineered to express cytokines. Failure of the immune system to destroy malignant cells is the result of either poor presentation of any available tumour antigens, as discussed earlier, or insufficient immunological activation. Therefore, many groups have attempted to create a locally increased level of immune activation within the tumour by transfer of cytokine genes directy into tumour cells[20]. In animal models, an enhanced immune response to weakly immunogenic tumours has been generated by *ex vivo* transfer of cytokine genes into tumour cells followed by immunization. This has been successfully accomplished by transfer of genes for IL-2, IL-4, IFN, TNF and granulocyte colony-stimulating factor[65]. Local secretion of a cytokine critical for activation of cytotoxic T lymphocytes can compensate for defects in the helper T cell arm of the immune system to permit recognition of the poorly immunogenic tumour by class I restricted cytotoxic T lymphocytes or other effectors of tumour cell clearance such as eosinophils and macrophages[66]. In animal models, poorly immunogenic tumours engineered to secrete IL-2 or IL-4 at high local concentrations generated tumour-specific cytotoxic T lymphocytes, which conferred systemic immunity against non-transfected tumour cells at distant sites[66–69]. This induction of immunological memory in cytotoxic T lymphocytes is pivotal if non-modified tumour cells at remote sites are also to be destroyed.

Different cytokines induce different immune effector mechanisms. For instance, the tumour infiltrate in a murine renal cell tumour secreting IL-4 consisted predominantly of macrophages and eosinophils, whereas the secretion of IL-2 by either a murine colon tumour line or a murine melanoma stimulated an MHC class I restricted cytotoxic T lymphocyte response against the parental tumour[66–69].

Although cytokine gene transfer offers an attractive approach to cancer vaccination, its use must be based on a clear understanding of both the tumour type and the immune response that the patient is able to mount against it. This may vary even between patients with the same tumour and obviously limits clinical adoption of this strategy. Finally, the choice of therapy should also be guided by the growth requirements of the tumour, as the local overproduction of certain cytokines can lead to enhanced growth of some tumours through an autocrine mechanism[70]. Thus the delivery of an inappropriate cytokine to tumour cells may actually promote aggressive cell growth. Work is under way to rationalize the use of cytokine gene transduction of tumour cells to produce optimal stimulation of tumour-infiltrating effector cells.

Gene correction therapy. The transformation of a normal cell never occurs in a single step and cannot be attributed exclusively to the mutation of only one gene[71]. Rather, there must be a series of mutations in several different genes that usually fall into one of at least two classes: the proto-oncogenes and the tumour suppressor genes[71]. In addition, mutations frequently occur in other classes of gene, which lead to acquisition of the metastatic phenotype[72].

Oncogenes are altered cellular genes encoding proteins that participate in normal pathways of cellular proliferation[22]. Tumour suppressor genes negatively regulate cell proliferation and promote cell differentiation[23]. Mutations in cellular proto-oncogenes lead to a dominant gain of function of the mutant protein, whereas deletions in tumour suppressor genes produce loss of function. These two genetic changes constitute part of the molecular basis of cancer development. Oncogenes are genetically dominant in that mutation in one of the two alleles is sufficient to induce neoplastic transformation. Tumour suppressor genes, however, require both alleles to be deleted or inactivated and function in a recessive manner. Whether or not these findings will contribute to new approaches in therapy remains speculative[73]. For this to be realistic requires either the abrogation of the activity of oncogenes or the replacement of tumour suppressor genes.

Oncogenes have been considered as targets for treatment both by rational drug design and by antisense oligonucleotide therapy. More than 60 oncogenes have been discovered and their protein products act at many different sites in the cell[22]. The elucidation of the crystal structure of one such protein, the oncogenic form of the *ras* protein, offers the chance to design a drug that will be highly selective in its action against mutant *ras* proteins while sparing normal *ras* proteins in non-cancer cells[74–76].

Antisense therapy is based on tumour-cell targeting of oligonucleotides that are complementary to the messenger RNA species encoding the oncogene products[77]. These oligonucleotides can be made highly specific by base pairing with the oncogene messenger RNA in the cancer cell, preventing translation (expression) of the oncoprotein product (*Figure 3*). *In vitro* studies have confirmed that antisense oligonucleotides directed against oncogenes can inhibit the growth of tumour cell lines, but major technical obstacles limit their application *in vivo*[73].

The challenges presented by tumour suppressors are different and require the delivery of correct copies of the missing gene to tumour cells. In this respect, clinical trials are under way to deliver a functional gene to replace a defective gene in T cells for adenosine deaminase deficiency and are also being considered for other genetic diseases, such as cystic fibrosis, Duchenne muscular dystrophy and the thalassaemias[31,78]. In cancer cells, this approach may ultimately prove to be more successful than current attempts to neutralize the effects of aberrantly expressed oncogenes[79,80], but the appropriate techniques are still remote. Reintroduction of the normal tumour suppressor genes *Rb*, p53 and *DCC* into appropriate

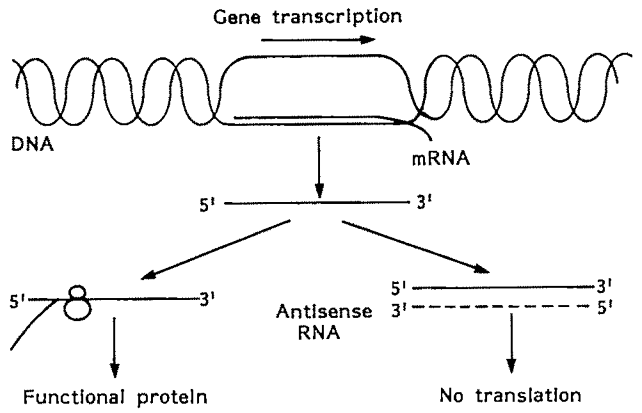

Figure 3 *Probable mechanism of action of antisense RNA. Binding to the messenger RNA prevents translation into functional protein*

tumour cell lines[79–82] has resulted in suppression of tumorigenicity and growth rates. However, replacement of these genes has not led to complete reversion to the untransformed phenotype nor has it been demonstrated to be a general phenomenon[23].

Despite encouraging experimental results of interventions directed against oncogenes and tumour suppressor genes, there remain major conceptual problems with their curative use. As carcinogenesis is a multistep process it is improbable that the correction of a single genetic defect will reverse the malignant phenotype. Indeed, by the time a patient presents to the clinic the dependence of tumour cells for their proliferation on any single genetic defect is very limited. Additionally, an absolute prerequisite for such therapy is the delivery of the therapeutic gene to all tumour cells in the body. Currently, no genetic delivery system can attain such efficiency. Thus, at present, it is difficult to conceive that correction of oncogene or tumour suppressor gene defects will achieve clinical realization in the short term other than as an adjunct to conventional therapy.

Delivery and targeting

The recurring shortfall of conventional cancer chemotherapy is the inability to deliver sufficient levels of a therapeutic agent specifically to all tumour cells while sparing their normal non-transformed counterparts. Similar problems exist for protocols of *in vivo* gene transfer to tumour cells, with one notable exception. In replacement of tumour suppressor genes or correction of oncogenes all malignant cells must be targeted. However, immunotherapy requires only that a significant fraction of either tumour cells or infiltrating cells is successfully transduced by gene transfer. Thereafter, the inherent specificity of the immune response to a given target antigen, together with its *in vivo* amplification, should result in efficient and accurate destruction of distant micrometastases.

The direct and specific delivery of therapeutic genes *in vivo* to tumour or infiltrating cells is an ideal that remains to be realized. This would obviate the need for the recovery, isolation and propagation of cells in culture while gene transfer is performed. Such protocols are time consuming and expensive but, more importantly, significant alterations in the phenotype of the recovered cells can occur during cellular adaptation to growth in culture.

Despite the efficiency and safety of retrovirus-mediated gene delivery, this method still lacks target-cell specificity. This property is conferred by the presence of cell membrane receptor proteins by which viruses gain entry into cells. Most viruses employ receptors that are expressed on a wide variety of cells, thus facilitating their propagation[83,84]. No known viruses infect exclusively tumour cells, although tumour cell-specific gene expression can be achieved with some viral vectors[85]. However, there are hopes that *in vivo* gene transfer will become a clinical reality as protocols already exist in which the gene is delivered directly into the tumour either by injection of DNA[64,86] or by administration of retrovirus stock[87].

In summary, the optimal protocol for gene transfer in the treatment of solid tumours currently involves the recovery of target cells (either tumour cells or the infiltrate) from the patient, their *ex vivo* expansion during which therapeutic gene transduction is achieved as efficiently and rapidly as possible by retroviral infection, followed by systemic administration of these altered cells back into the patient.

Patient selection

Preclinical studies in animal models have indicated that active immunization to pre-existing tumours is most effective when the tumour load is small and less effective against widespread cancer[67,88]. As a result, many investigators have proposed that, optimally, such therapies should be given early in the treatment of patients with cancer[65,89]. Clinical evidence for this seemingly rational proposal, although scant, does suggest that these treatments appear to be most effective in patients with early disease[90,91]. Most clinical studies of active specific immunization against cancer have been performed in patients with advanced tumours, so anything other than a dramatic response to therapy is likely to be concealed[32]. These protocols are ethically sound as such patients have failed to benefit from any other form of treatment, either alone or in combination. It is therefore appropriate that these, often young, patients with end-stage cancer should be offered the opportunity to participate in the initial clinical studies, provided that such novel therapy does not itself result in additional morbidity.

If the initial promise of these innovative strategies is to be translated into clinical reality there must be major changes in patient selection. Therapeutic gene transfer in patients with cancer ultimately needs to be brought into the context of adjuvant therapy[89,92], i.e. in the treatment of patients with minimal residual (microscopic) disease following radical resection of a primary tumour. Clearly, such a policy poses many ethical issues that must now be addressed. Not least of these is the problem of exposing relatively healthy patients to experimental therapies.

Evaluation of the results of these treatment protocols will require the definition of clear response endpoints, as initial tumour regression is not always associated with increased survival[89]. It is improbable that any of the therapeutic regimens discussed will be effective in isolation, given the complexity of host–tumour immune interactions. A combined approach will almost certainly be required, involving existing therapy and manipulation of both tumour cells and the immunological infiltrate[18,93,94].

Despite significant advances in the understanding of the molecular basis of cancer and the immunological response that a tumour elicits, widespread clinical application of this work is remote. However, it has become clear that gene transfer is, at the very least, a realistic treatment adjunct in some patients with cancer. Such therapies are currently in their infancy but the results of experimental studies have already been translated into clinical practice. Six gene therapy trials using retrovirus-mediated gene transfer in the treatment of patients with solid tumours have been established in the USA[31]. These trials have been approved by the Recombinant DNA Advisory Committee of the National Institutes of Health and the safety of such approaches is now widely accepted[31]. The benefits of treating selected patients with solid tumours with tumour-infiltrating lymphocytes are clear, but it remains to be seen whether using gene-modified tumour or infiltrating cells can improve on these results. Laboratory-based work has provided some clear strategies for the future in this field; the next decade will reveal whether they are to be of real value to patients with cancer.

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Modern management of pancreatic pseudocysts

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Pseudocysts may develop as a complication of acute pancreatitis, chronic pancreatitis or pancreatic trauma. As new methods of imaging provide fuller information on their incidence and natural history, important differences are emerging between the pseudocysts of acute and chronic pancreatitis. Traditional surgical approaches to the management of pseudocyst are now being challenged by endoscopic techniques and interventional radiology. In the light of these developments the options available are reviewed and strategies for the modern management of pancreatic pseudocysts are suggested.

A pancreatic pseudocyst is a fluid collection that arises in or adjacent to the pancreas but lacks an epithelial lining. True cysts of the pancreas, which are either congenital or neoplastic, possess an epithelium. Such cysts constitute only 15 per cent of all cystic lesions of the pancreas[1,2] and are therefore greatly outnumbered by false cysts (pseudocysts), which are inflammatory in origin. The inflammation may be due to acute or chronic pancreatitis or may follow trauma.

Historical developments

Pseudocyst of the pancreas was originally described by Morgagni[3] in 1761. Its successful surgical management was reported in 1882 by Bozeman[4], who excised a 10-kg pseudocyst from the 41-year-old wife of a prominent Texan physician. The following year the first drainage procedure was undertaken by Gussenbauer[5], who marsupialized a pseudocyst to provide external drainage. Transgastric pseudocystogastrostomy[6] was described in 1921, pseudocystoduodenostomy[7] in 1928 and pseudocystojejunostomy[8] in 1931.

Although surgical drainage remains the principal method of treating pseudocysts, its pre-eminence has recently been challenged. Percutaneous drainage of uncomplicated pseudocysts may now be carried out under ultrasonographic or computed tomographic guidance[9]. Percutaneous pancreatic cystogastrostomy has been performed by placing a tube with suitable sideholes through the stomach into the cyst cavity[10]. Pseudocysts adjacent to the stomach and/or duodenum have been drained endoscopically by using diathermy to create an internal fistula[11,12]. More recently, cyst drainage has been achieved by endoscopic placement of transpapillary catheters across ductal disruptions into pancreatic or peripancreatic fluid collections[13].

These new and imaginative therapies compete with the traditional operative treatment of pancreatic pseudocysts. Current management strategies are controversial and are the subject of this paper. First, it is necessary to review the different types of pseudocyst and their natural history. Thereafter, different treatment options are considered together with personal case reports to illustrate some of their drawbacks.

Classification and incidence

Pseudocysts were once considered to be an unusual complication of pancreatitis. As recently as 1968 Becker and colleagues[14] wrote: 'the experience (with pseudocysts) in most large surgical clinics is limited to relatively few patients'. The advent of ultrasonography[15] and computed tomography (CT)[16] has shown that the prevalence of pseudocyst after an attack of acute pancreatitis ranges from 16 to 50 per cent[17,18]. Incidence figures of 20–40 per cent have been reported for pseudocysts in chronic pancreatitis (see below). Although pancreatic pseudocysts are a common complication of both acute and chronic pancreatitis, their pathogenesis and natural history seem to be different in the two settings. The relative proportion of acute and chronic pancreatic pseudocysts varies between reports, and when alcohol is the commonest cause of acute pancreatitis (as in several American series) the distinction is blurred[16,17,19,20].

The underlying cause of the pseudocysts also varies between series[17,21,22]. One American report of 69 pseudocysts noted that 78 per cent were related to alcoholic pancreatitis, 7 per cent to complicated gallstone pancreatitis, 6 per cent were of unknown causation (idiopathic) and 3 per cent each were due to trauma, hyperlipidaemia or a recent surgical operation[17]. A similar study of 83 patients from South Africa included 70 per cent of cysts that followed alcohol-associated pancreatitis, 22 per cent that were due to blunt abdominal trauma and 8 per cent that were idiopathic[21].

From this experience D'Egidio and Schein[21] proposed a classification that differentiates between the pseudocysts of acute and chronic pancreatitis, identifying three distinct types. Type I or acute 'postnecrotic' pseudocysts occur after an episode of acute pancreatitis, are associated with normal duct anatomy and rarely communicate with the pancreatic duct. These cysts should be monitored by serial scans, and intervention is reserved for those that increase in size or persist beyond 4 weeks. Type II, also postnecrotic pseudocysts, occur after an episode of acute-on-chronic pancreatitis. The pancreatic duct is diseased but not strictured, and there is often a duct–pseudocyst communication. Internal drainage is usually required. Type III, defined as 'retention' pseudocysts, occur with chronic pancreatitis and are uniformly associated with duct stricture and pseudocyst–duct communication. Surgical procedures for type III cysts must address the underlying duct pathology.

We broadly agree with this classification and management outline, but the distinction between acute-on-chronic (type II) and chronic (type III) cysts can be subtle. It often requires operation to show the presence of necrotic debris, indicating a recent flare-up of acute-on-chronic pancreatitis that may have been missed clinically. Whenever possible the pancreatic duct should be delineated in patients with chronic pseudocysts, since an independent surgical approach may be required to deal with underlying duct pathology. In our experience, however, on-table pancreatography often fails to confirm duct–cyst communication in such cases and there may be generalized ductal ectasia without stricture.

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Acute pancreatitis

In the context of acute pancreatitis a pseudocyst may be defined as a loculated effusion, rich in amylase, that develops in the vicinity of the pancreas, usually within 2 weeks of the onset of an attack[23]. It is thought to be associated with disruption of a pancreatic duct, allowing the escape of pancreatic secretions into peripancreatic tissues and planes. A peripancreatic collection might also follow leakage of juice from the inflamed surface of the gland, analogous to the pleural effusion that complicates pneumonia. Although in our experience a communication can seldom be demonstrated between the pseudocyst and the pancreatic ductal tree when endoscopic retrograde ductography or on-table cystography is performed[24], it is possible that a small ductal leak could initiate cyst formation and then seal with the passage of time.

The pseudocysts of acute pancreatitis are essentially extrapancreatic in site, often contained within the lesser sac (omental bursa) but sometimes further afield (e.g. within the leaves of the lesser omentum) or even remote within the mediastinum or pelvis[25,26]. Most peripancreatic fluid collections that follow an attack of acute pancreatitis will resolve unless they become infected or contain large quantities of necrotic tissue[27]. Using ultrasonography, Bradley and colleagues[28] found acute fluid collections within the lesser sac in 52 of 92 patients (57 per cent) with a clinical diagnosis of acute pancreatitis. A much scarcer entity, the late pseudocyst comprises a persistent localized collection of enzyme-rich fluid with a clearly defined wall made of fibrous tissue and adjacent viscera; this complication arises in only 2–7 per cent of patients with acute pancreatitis[29,30].

Chronic pancreatitis

The pathogenesis of pseudocyst formation in chronic pancreatitis is uncertain, but at least two mechanisms might be involved. First, the cyst might develop as a consequence of an acute exacerbation of the underlying disease, in which case serial scans should reveal its formation after a more severe attack of pain, perhaps accompanied by transient increases in serum amylase levels. This explanation fits cysts that are diagnosed after an attack of acute-on-chronic pancreatitis and contain necrotic debris. Second, blockage of a major branch of the pancreatic duct by a protein plug, calculus or localized fibrosis could lead to rupture of the acini draining that segment of the gland. This process would develop insidiously, although the cyst itself might become a source of pain once it had reached a sufficient size. This explanation fits those cysts that are found incidentally on investigation of a patient with chronic pancreatitis and that contain clear fluid.

The pseudocysts of chronic pancreatitis are generally intrapancreatic in site, especially the variety that develops insidiously. Even if they reach considerable size, they appear to be contained within a prolongation of the pancreatic capsule. Thus, the lesser sac tends to be obliterated by acute pancreatic pseudocysts but remains patent, at least in part, with chronic pancreatic pseudocysts. Again, duct communication with the cyst cannot always be identified radiologically in chronic pancreatitis, possibly because the duct or ductules become completely obstructed. Using endoscopic retrograde cholangiopancreatography (ERCP) and on-table pancreatography, it was noted that only five of 21 chronic pseudocysts communicated with the main pancreatic duct (MPD)[24]. Others have found a much higher incidence of pseudocyst–MPD communication (44–68 per cent) on preoperative ERCP[31–33]; Nealon and colleagues[33] suggested that the incidence of communication was similar in acute and chronic pancreatitis. Pseudocysts may be detected by scanning in approximately 20 per cent of patients with symptomatic chronic pancreatitis[34,35] and in one study were found at operation in 34 of 87 patients (39 per cent) undergoing longitudinal pancreatojejunostomy[36].

Traumatic pseudocysts

Pseudocysts may develop in the aftermath of pancreatic trauma, a condition that may be likened to traumatic cyst of the spleen. Although adult series of pseudocysts report trauma as the aetiological factor in only 3–8 per cent of patients[17,37], most pancreatic pseudocysts in children are post-traumatic[38,39]. The typical picture is of a patient who develops abdominal pain and a raised serum amylase level following a blunt injury to the upper abdomen and is then found to have a cystic swelling 1–2 weeks later. The cyst fluid has a high amylase content. Either the cyst develops as a result of leakage from a duct or ductules disrupted by the blow or, perhaps, haematoma following contusion of the gland turns into a collection of pancreatic juice as the blood is resorbed and replaced by seepage from a capsular tear.

Natural history

Presentation

The widespread application of ultrasonography and CT has advanced knowledge of the natural history of pancreatic pseudocysts. Previously, the diagnosis was based on clinical suspicion, as follows: (1) failure of an episode of acute pancreatitis to resolve within 7–10 days; (2) presence of an epigastric mass; (3) persistently raised serum amylase level; (4) onset of sepsis of probable intra-abdominal origin; (5) obstructive symptoms such as jaundice or vomiting; and (6) evidence of marked anterior displacement of the barium-filled stomach or colon[14,15]. Some 90 per cent of patients with pseudocysts have persistent abdominal pain[14,40], and up to half have nausea, vomiting, and weight loss[41]. An abdominal mass is palpable in 43–56 per cent[14,42].

Spontaneous resolution

Earlier studies suggested that spontaneous resolution of an acute pseudocyst occurred in 8–30 per cent of patients[19,43]. In an older study[44], which inferred the presence of pancreatic pseudocysts from barium meal studies or angiography, over 70 per cent of pseudocysts appeared to resolve spontaneously within 3–12 weeks. The ultrasonographic survey of Bradley and colleagues[15] in Atlanta, USA, could confirm the clinical diagnosis of a pseudocyst in only 93 of 189 patients (49 per cent), thus emphasizing the inaccuracy of an unsupported clinical diagnosis. This survey followed the natural history of pseudocysts in 93 patients, 31 of whom had acute pancreatitis and 62 chronic disease. Spontaneous resolution occurred in ten of 24 patients in whom a pseudocyst was present for <6 weeks. By contrast, of 13 pseudocysts that had been present for 7–12 weeks, only one resolved spontaneously. Spontaneous resolution did not occur at all in the remaining 12 patients followed for up to 18 weeks. The clear implication was that pseudocysts still present at 6 weeks are unlikely to resolve spontaneously. Moreover, the incidence of complications correlated directly with the length of time the pseudocyst was present: 20 per cent of patients with early pseudocyst (<6 weeks) had a complication, as opposed to 46 per cent with cysts that were 7–12 weeks old and 75 per cent of those with chronic cysts (beyond 13 weeks)[15].

More recently, Yeo and colleagues[16] in Baltimore, USA, used serial CT to observe the natural history of pancreatic pseudocysts in 75 patients; their findings challenge the conclusion of Bradley and colleagues that delay is at best fruitless and at worst hazardous. Seventy-one patients had a history of acute pancreatitis and 39 chronic pancreatitis[16]. Thirty-nine patients underwent operation at a median of 75 days from the onset of symptoms. The indications for operation were abdominal pain (62 per cent), inability to tolerate oral intake (3 per cent), enlargement of the pseudocyst on CT (18 per cent) or a complication such as infection (8 per cent), haemorrhage (5 per cent) or rupture of the pseudocyst (3 per cent). Thirty-six patients who were asymptomatic were managed without operation and were observed for a mean of

1 year. Of these, 60 per cent had complete resolution of the pseudocyst and 40 per cent had pseudocysts that remained stable or reduced in size. Only one patient of the 36 treated expectantly (i.e. without operation) developed a complication from the pseudocyst in the form of transient intracystic haemorrhage.

The size of the pseudocyst was an important predictor for operative drainage in the experience of Yeo and colleagues[16]: 67 per cent of pseudocysts $\geqslant 6$ cm in diameter required surgical treatment, as opposed to 40 per cent of those <6 cm in size. Similarly, O'Malley and colleagues[17] noted that pseudocysts of <4 cm resolved spontaneously at a mean of 2·6 months after diagnosis, although in one case resolution did not occur until 28 months. It would appear, therefore, that smaller asymptomatic cysts can be managed safely by observation and do not require surgical intervention even if they are still present after several months. If the cyst is symptomatic, enlarging or >6 cm in diameter, intervention is indicated.

Acute and chronic pseudocysts

It is generally agreed that acute and chronic pseudocysts have a different natural history, but relatively few authors have attempted to analyse these groups separately[28,40,45] and many reports do not differentiate between pseudocysts that complicate acute pancreatitis and those that complicate chronic disease. The position is further confused because initial assumptions as to the aetiology of a pseudocyst may be erroneous. Nealon and colleagues[33] recognized that nine of 41 patients thought to have acute pancreatitis with pseudocyst actually had chronic pancreatitis on the basis of ERCP findings. Others have identified the typical features of chronic pseudocysts on CT: such cysts are oval or spherical in shape, arise within the pancreatic parenchyma (which is frequently calcified) and usually have a sharp margin or interface with the surrounding tissue[46].

Crass and Way[40] compared the natural history of 22 acute pseudocysts with that of 46 chronic lesions. An acute pseudocyst was diagnosed within 2–6 weeks of an episode of pancreatitis, while a chronic pseudocyst was defined as an established lesion with no recent episode of pancreatitis. It should be noted that using this definition means that some patients with an acute pseudocyst have chronic pancreatitis, i.e. permanent damage to the underlying gland. Spontaneous resolution occurred in three of the 22 acute and in none of the chronic pseudocysts. Internal drainage was possible in only nine of 19 patients undergoing operation for an acute pseudocyst but in 34 of 35 having elective operation for chronic pseudocyst. The mortality rate in the patients with acute pseudocysts was 25 per cent, compared with 4 per cent in those with chronic cysts. A similar British experience included 12 deaths among 86 patients with acute pseudocysts and no deaths in a group of 14 with chronic pseudocysts[30]. In this study the mortality rate for acute pseudocysts complicating gallstone pancreatitis was four times that following alcoholic pancreatitis.

The transient nature of some acute pseudocysts allows a more expectant policy of management to be adopted than would be appropriate for chronic pseudocysts. Crass and Way[40] recommended that acute pseudocysts be drained, internally if possible, after a 6-week period of observation, but that immediate operation should be performed for chronic pseudocysts, since delay only exposes the patient to the risk of complications and there is a negligible chance of spontaneous resolution. In support, Bradley and co-workers[28] observed a higher spontaneous resolution rate (25 per cent) in a group of 38 patients with acute pseudocysts but noted an appreciable mortality rate (10 per cent) and morbidity rate (24 per cent) in 41 with chronic pseudocysts managed by observation.

Can non-resolution of a cyst be predicted? Warshaw and Rattner[45] divided 42 patients with pseudocysts as follows: chronic pancreatitis 20, acute pancreatitis 14, acute-on-chronic pancreatitis eight. Spontaneous resolution occurred in only three patients, all of whom had acute pancreatitis and a free communication with a normal MPD. The size of the cyst did not affect the chance of resolution, but no cyst present for >6 weeks resolved. They concluded that the following criteria suggest that a pseudocyst will not resolve spontaneously: (1) persistence for >6 weeks; (2) evidence of chronic pancreatitis; (3) pancreatic duct abnormality other than communication with the pseudocyst; and (4) ultrasonographic suggestion of a thick wall.

Timing of intervention

The timing of intervention is a critical matter that requires considerable judgement. The pseudocysts of chronic pancreatitis can be drained surgically as soon as they are diagnosed, in the confident expectation of finding a mature cyst wall capable of holding sutures[45]. Infected pseudocysts require immediate external drainage by the simplest means available. The optimal timing of intervention in acute or traumatic pseudocysts is more difficult to determine[46]. If operation is undertaken too early the pseudocyst wall will be friable and unable to hold sutures, necessitating external drainage with its attendant increase in morbidity and mortality rates[37,47]. If the operation is delayed unduly the incidence of complications will rise, as suggested by some workers[15] if not by others[16].

Studies in dogs have shown that a period of 6 weeks is required for development of a mature pseudocyst wall[48]. Several authors have used a 4-week waiting period with good results[15,42,49]. The consensus is that a minimum of 4–6 weeks from the time of diagnosis of an acute pseudocyst is required for the wall to become sufficiently mature for safe internal drainage[24,41]. If infection or pressure symptoms demand decompression of the cyst before that time (and this is unusual), external drainage can be performed either percutaneously or at operation. The hazards of premature cystogastrostomy are illustrated by the following case.

Patient 1. A 53-year-old woman developed an enormous retrogastric pseudocyst after an attack of gallstone pancreatitis. Continuing pain and fever led to laparotomy, cholecystectomy and cystogastrostomy 16 days after admission. At operation the cyst contained 1 litre turbid watery secretions, but there was no necrotic or particulate debris. Thereafter the patient became pyrexial and needed a second operation 2 weeks later to debride an abscess in the cyst cavity. Persistent sepsis led to a third exploration 4 weeks after admission, which revealed an omental abscess and an inflammatory mass of jejunum adherent to the head of the pancreas. The mass was bypassed by means of enteroenterostomy and two tubes were placed into the cyst cavity to drain a gastric fistula externally. During a stormy postoperative course the patient required parenteral nutrition and cyst lavage via the tube drains. After 2 months the drainage from the cyst diminished sufficiently for her to be allowed home (19 weeks after admission). Although diabetic, she remains well 6 years later.

Warshaw and Rattner[45] have suggested that the presence of a serum isoamylase, called 'old' amylase, in a patient with a pseudocyst may be a reliable indicator for successful internal drainage. In an analysis of 19 patients, nine with acute and ten with chronic pseudocysts, they found that internal drainage was possible in all 14 patients with 'old' amylase and not possible in four of five without. However, they found considerable overlap when they attempted to correlate the presence of 'old' amylase with the chronological age of the pseudocyst and noted that 'old' amylase was not universally present in chronic pseudocysts. They concluded that the appearance of 'old' amylase in the serum was the signal for safe internal drainage. Future studies would be useful to confirm these findings. Meantime, it is our policy to monitor these patients with serial CT and, whenever possible, to try to delay surgical drainage for 5–6 weeks.

Non-operative options

Improved imaging plus new percutaneous and endoscopic techniques for draining pseudocysts are challenging the previous hegemony of the surgeon. The new methods include percutaneous drainage under ultrasonographic or CT guidance, endoscopic cystogastrostomy and cystoduodenostomy, and endoscopic transpapillary stenting.

Percutaneous drainage

Diagnostic percutaneous aspiration of peripancreatic collections is readily performed under ultrasonographic or CT control[9], but needle aspiration alone is generally an ineffective therapy[9,50,51]. Simple aspiration of pseudocysts carries a 70 per cent recurrence rate[41], and repeated aspiration theoretically introduces a cumulative risk of complications. The inadequacy of percutaneous aspiration alone is shown by the following case.

Patient 2. Following a kick from a horse a 15-year-old girl developed traumatic pancreatitis and a left-sided pseudocyst. She became pyrexial with vomiting and abdominal pain and was treated conservatively. At 3 weeks after the injury cystogastrostomy was performed, but 1 week later recurrence of the cyst was heralded by further vomiting. During the next 3 weeks three percutaneous cyst aspirations produced respectively 48, 140 and 215 ml fluid rich in amylase. Persistence of the cyst led to reoperation 1 month after the cystogastrostomy. A large pseudocyst within the lesser omentum was drained by a retrocolic Roux-en-Y cystojejunostomy. On-table cystography had failed to demonstrate a communication with either stomach or pancreas. The patient remains well 5 years later.

Although in our opinion needle aspiration is inappropriate primary treatment for acute pseudocysts (except as a temporary measure), percutaneous catheter drainage deserves closer scrutiny. Insertion of a pigtail catheter allows the cyst to remain collapsed, and up to 90 per cent of pseudocysts may be drained successfully in this way[52]. The effectiveness and necessary duration of percutaneous drainage seem to be related to the presence of a communication between the pancreatic duct and the pseudocyst. Such a communication can be demonstrated by endoscopic retrograde or percutaneous pancreatic ductography or by subsequent cystograms obtained down the catheter track. Simple aspiration will not resolve communicating cysts, and catheter drainage must be prolonged in such cases. D'Egidio and Schein[53] treated 23 pseudocysts by percutaneous catheter drainage in 21 patients. All 13 pseudocysts without ductal communication (type I) resolved after drainage for a mean of 16 (range 11–23) days while nine of ten type II pseudocysts resolved after drainage for a mean of 24 (range 19–47) days. Similarly, in a series of 77 patients with 101 pseudocysts of mixed aetiology, van Sonnenberg and colleagues[52] reported successful obliteration of 90 per cent of the pseudocysts after drainage for a mean of 19·6 days. In a subgroup of 34 patients in whom a fistula was demonstrated, drainage was required for a mean of 28·3 days for pseudocyst obliteration. In ten patients (13 per cent) catheter drainage failed. Six of them underwent operation for persistent catheter drainage, while four cysts that recurred after catheter dislodgement were successfully redrained percutaneously.

An infected pseudocyst should be drained as an emergency. These patients generally have toxaemia, and the clinical improvement that follows drainage can be dramatic[52]. Increasing size (>4–5 cm) and the onset of signs of obstruction (vomiting, jaundice) or infection are indications for intervention in non-infected pseudocysts. In the series of van Sonnenberg and colleagues[52], the mean duration of drainage for infected pseudocysts was 17 days and for non-infected cysts 21 days. Complications occurred in ten of 77 patients (13 per cent) and included bacterial superinfection or colonization of previously sterile pseudocysts (8 per cent), pneumothorax (1 per cent), pleural effusion (1 per cent) and minor haemorrhage (3 per cent). There has been one death reported from inadvertent percutaneous placement of a catheter into a large pseudoaneurysm in a patient with pancreatitis[54].

Retroperitoneal, transperitoneal, transgastric, transhepatic and transduodenal routes may all be used for percutaneous pseudocyst drainage with comparable results[52]. The transgastric approach has a theoretical advantage if endoscopic or percutaneous ductography has demonstrated an occluded pancreatic duct. In this situation antegrade flow through the pancreatic duct is impossible, and a pseudocyst–gastric fistula may develop along the catheter to allow internal drainage[52]. Matzinger and colleagues[55] obtained complete resolution in eight of 12 patients with pseudocysts treated by a percutaneous transgastric approach. Two patients required operation, one for infection after drainage and one for cyst recurrence.

Hancke and Henriksen[10] have performed percutaneous pancreatic cystogastrostomy using a combination of ultrasonography and gastroscopy to place a double-pigtail catheter percutaneously so that one curled end lay in the pseudocyst and the other in the stomach. They used this technique successfully in 16 of 18 patients and observed neither serious complications nor pseudocyst recurrence.

Endoscopic drainage

Chronic pseudocysts impinging on the gastric or duodenal wall may be drained endoscopically by creating a fistula between the cyst and the relevant viscus[12]. The cyst is initially punctured through the gut wall, following which a diathermy needle or 'sphincterotomy' wire is used to create a 1–2-cm opening. Both endoscopic cystogastrostomy and endoscopic cystoduodenostomy have been performed using this technique. Cremer and co-workers[56] achieved pseudocyst drainage with endoscopic cystogastrostomy in all ten patients with chronic pancreatitis so treated. However, two patients had serious complications: arterial bleeding and infection in one and infection alone in the other. Neither patient required operation; the bleeding was controlled by endoscopic electrocoagulation and the infections were treated by endoscopic cyst–gastric stenting and percutaneous drainage. In another report, although the pancreatic pseudocyst decreased in size following endoscopic transgastric drainage, the patient died from septicaemia[11]. A further report of life-threatening haemorrhage following endoscopic cystogastrostomy emphasizes the need for careful preparation and adequate surgical support when performing these new interventions[57].

Cremer and colleagues[56] also successfully drained 21 of 22 pseudocysts by endoscopic cystoduodenostomy without serious complications. By contrast, Sahel and co-workers[12] reported five serious complications in a series of 19 patients in whom this technique was performed for cysts associated with chronic calcific pancreatitis. Bleeding occurred in two patients, one of whom died as a result. Two patients had duodenal perforation, which was managed conservatively, and there was one episode of transient cholangitis. The safety of internal endoscopic drainage thus remains to be established.

Endoscopic transpapillary approaches

Kozarek and colleagues[13] used transpapillary duct stents to treat 18 patients with persistent pancreatic duct disruption associated with symptomatic peripancreatic fluid collections (14) and including 12 patients who had undergone previous drainage, either percutaneous (eight) or surgical (four). Having identified duct disruption by endoscopic pancreatography, they placed a guidewire via the endoscope through the papilla and across the disrupted pancreatic duct. A 5–7-Fr polyethylene stent was then positioned across the ductal disruption (preceded by a nasopancreatic drain in two cases). A sphincterotomy was required to facilitate this manoeuvre in only three patients.

Initial results in this series were excellent; 16 of 18 duct disruptions and 12 of 14 peripancreatic fluid collections resolved. However, at a median follow-up of 16 months seven patients had required operation for continuing pancreatic pain or residual/recurrent fluid collection. Moreover, two patients had immediate, albeit mild, exacerbation of symptoms of pancreatitis after stent placement; another two whose stents occluded had recurrent pancreatitis and one developed a duct stenosis. The development of local stenoses and side branch ectasias that resemble chronic pancreatitis is a more serious complication of transpapillary pancreatic stent placement[58], and Kozarek and colleagues[13] noted minor duct changes in 50 per cent of the patients restudied at the time of stent retrieval.

Summary

Viewed from a surgical standpoint, these new non-operative techniques increase the therapeutic armamentarium available for acute pseudocysts but certainly do not render operation obsolete. Needle aspiration seems unlikely to 'cure' anything other than small and non-communicating cysts that might well have resolved with time in any event. Percutaneous catheter drainage has the same potential drawback as external surgical drainage, namely that a pancreatic fistula may persist in the presence of continuing inflammation or a connection with the main ductal tree. Endoscopic fashioning of an internal communication with the stomach or duodenum is more attractive because it recreates the surgical ideal of permanent internal drainage. Unfortunately, it is emerging as the non-operative technique with the highest rate of troublesome complications including death. Endoscopic transpapillary stent placement facilitates internal drainage, but is suitable only in patients with identifiable duct disruption. Long-term results are not encouraging, and the wide application of this technique cannot be recommended at this stage.

Surgical options

The operative management of pancreatic pseudocysts aims to evacuate the cyst contents and prevent the serious complications of cyst rupture, haemorrhage, infection and intestinal obstruction[14]. If the cyst cavity is decompressed, it is likely to become obliterated with the passage of time. For acute pancreatitis there is a choice between external and internal drainage, but in chronic pancreatitis there is also the possibility of cyst resection. The cyst is only one feature of the underlying disease, and the decision between resection and drainage will be influenced by features such as the extent of surrounding inflammation, vascular involvement and duct ectasia.

External drainage

This is the simplest method of draining a pseudocyst, but carries a mortality rate of 6 per cent and a recurrence rate of 22 per cent[2]. These figures probably reflect the severity of pancreatitis in the patients chosen for external drainage rather than the specific shortcomings of the technique. External drainage is the operation of choice for grossly infected cysts, those associated with haemorrhage or free rupture necessitating emergency laparotomy, and immature cysts with a soft wall that will not hold sutures. As already stated, there may be non-operative alternatives that are preferable in several of these situations. A persistent pancreatic fistula may be anticipated in 10 per cent of patients following external drainage[29]. When fistulas fail to close, usually because of proximal pancreatic duct obstruction, either distal pancreatectomy or drainage of the fistula by means of a Roux loop of jejunum may be necessary[41].

Internal drainage

Internal drainage establishes a controlled fistula into the gastrointestinal tract and is the method of choice for all mature uncomplicated pseudocysts. Cystogastrostomy and cystojejunostomy are alternative procedures for establishing internal decompression[37]; cystoduodenostomy is occasionally indicated for a small cyst in the pancreatic head[59]. Overall, internal drainage is associated with a mortality rate of 2 per cent and a recurrence rate of 5 per cent[2].

Choice of operation

Controversy surrounds the question of which viscus should be used for pseudocyst drainage: stomach, duodenum or a Roux loop of jejunum. Anatomical considerations sometimes dictate the choice; for example cystogastrostomy is inappropriate unless the stomach is closely applied to the front of the cyst. For the rest it is a matter of the surgeon's preference, our own being to use a Roux loop of jejunum because of its versatility. Likewise we prefer jejunum to stomach for duct drainage procedures in chronic pancreatitis, or indeed for pancreatic anastomosis after proximal pancreatectomy.

Preoperative ERCP has been used to refine operative strategy. Nealon and co-workers[33] successfully carried out ERCP in 39 of 41 patients with pseudocysts, 15 with acute and 26 with chronic pancreatitis; there were no complications of the procedure. On the basis of ERCP findings the operative plan was changed in 24 of the 41 patients, thereby improving outcome. In a similar series of pseudocysts of various aetiology, preoperative ERCP influenced the choice of operation in nearly half (19 of 39 patients)[31]. Sepsis was a rare complication (two patients) and occurred only when operation was delayed for >24 h. From a retrospective analysis of 102 patients, Ahearne and co-workers[60] advocated an ERCP-based algorithm for the management of pseudocysts. The presence of pancreatic duct obstruction or pseudocyst communication was an indication for operation. Treatments that followed the algorithm had a lower incidence of adverse outcome than those that did not (12 *versus* 43 per cent, $P < 0{\cdot}04$). Thus valuable information that can influence management strategies may be obtained by ERCP, although peroperative cystography and/or ductography can provide similar or supplementary data[24].

Cystogastrostomy

Transgastric cystogastrostomy is a relatively simple approach that exploits the fact that many mature cysts are densely adherent to the posterior wall of the stomach. The cyst is approached through the lumen of the stomach, the margins of the posterior gastrostomy being oversewn in the manner of an anastomosis. Objections to cystogastrostomy are that the cyst is not always contained within the lesser sac nor always adherent to the stomach. The anastomosis may not produce dependent drainage if the cyst is large and extends below the greater curve. Johnson and colleagues[61] noted that the complication rate following cystogastrostomy was directly proportional to the size of the pseudocyst. Three of four patients with giant pseudocysts (>15 cm) had life-threatening complications as a result of incomplete emptying of the cyst, and two of them died. Moreover, entry of gastric contents into the cyst cavity may occasionally lead to further complications including haemorrhage, pancreatic abscess, gastric fistula and cyst recurrence, as illustrated below.

Patient 3. A 57-year-old man with severe gallstone pancreatitis developed a large pseudocyst arising from the head and body of the pancreas and extending to the left loin. Cystogastrostomy was carried out 11 weeks after the onset of symptoms. A pancreatic abscess was drained 1 week later through the left loin; this was followed by two episodes of severe secondary haemorrhage, one of which necessitated packing of the wound. At 1 month after cystogastrostomy the man developed a gastric fistula via the cyst cavity to the left loin wound; total parenteral nutrition was commenced. After a further week he had haematemesis, associated with peritonitis and a third catastrophic haemorrhage from the loin wound. At emergency laparotomy erosion of the splenic artery was found and splenectomy was performed. His condition deteriorated and the man died 10 days after operation.

Cystojejunostomy Roux-en-Y

Recent reports indicate that cystojejunostomy Roux-en-Y is now performed for internal drainage of pseudocysts more frequently than cystogastrostomy[17,22,31,62]. The Roux loop can be anastomosed to the lower part of the cyst, using an approach through the transverse mesocolon for a collection in the lesser sac. It is likely that dehiscence of a cystojejunostomy has less serious consequences than that of a cystogastrostomy, provided that a Roux loop is used (although this entails a second anastomosis). Few authors have compared the results of the two procedures, but Newell and colleagues[62] have recently reported 39 patients who underwent cystogastrostomy and 59 who had cystojejunostomy for elective internal drainage of a pseudocyst. The two groups were comparable for age, sex, cause of pancreatitis and pseudocyst location. There was no significant difference in mortality rate between the two groups (5 *versus* 3 per cent). Cystogastrostomy was associated with a shorter operative time, reduced peroperative blood loss and lower fluid requirements. The hospital stay was also shorter after cystogastrostomy (11 *versus* 19 days). By contrast, complications were slightly more frequent; the incidence of cyst recurrence was 10 per cent after cystogastrostomy and 8 per cent after cystojejunostomy, while the incidences of postoperative gastrointestinal haemorrhage were 7 and 2 per cent respectively.

The same tendency towards a higher complication rate after cystogastrostomy emerges from three other series. Schattenkerk and associates[59] described complications in four of seven patients (ileus two, bleeding one, abscess one) undergoing cystogastrostomy but in none of six with cystojejunostomy. Likewise, Frey[37] observed that nine of 24 patients required reoperation because of recurrence of pain after cystogastrostomy compared with three of 13 after cystojejunostomy. In another series there were only two recurrent cysts in 42 patients after cystojejunostomy and neither patient required reoperation[22]. Our own recent experience tends to favour cystojejunostomy. In seven patients referred to this unit, transgastric decompression had failed to deal adequately with a pancreatic pseudocyst. All seven required reoperation for one or more of the following complications: gastrocutaneous fistula (five cases), haemorrhage (four), abscess formation (three) and anastomotic occlusion (two); one patient died. Four of these patients are described in the case reports in this review. We therefore caution against the indiscriminate use of cystogastrostomy and advocate cystojejunostomy for the definitive treatment of mature pancreatic pseudocysts.

Cystoduodenostomy

Cystoduodenostomy is rarely indicated. It should be reserved for pseudocysts in the head of the pancreas that impinge on to the duodenal wall[14]. This procedure is likely to be appropriate only in relatively small cysts that complicate chronic pancreatitis. Care must be taken not to injure the intrapancreatic common bile duct or the gastroduodenal artery. Cystoduodenostomy carries a 5 per cent mortality rate and a 5 per cent recurrence rate[14].

Complications of internal drainage

Upper gastrointestinal haemorrhage is the most frequent complication of internal cyst drainage. It occurs in about 12 per cent of cases and is associated with a high mortality rate[19,37,62,63]. Frey[37] reported upper gastrointestinal haemorrhage after cystogastrostomy in three of 24 patients, two of whom died; others confirm a high mortality rate of 50–66 per cent[19,62]. The source of bleeding may be the edge of the cystogastrostomy, the gastric mucosa or a pseudoaneurysm in the depths of the cyst cavity[37].

Pseudoaneurysm was the source of bleeding in 13 of 120 patients (11 per cent) undergoing cystogastrostomy in Frey's series of pancreatic pseudocysts[37]. This experience led him to advocate preoperative angiography of the superior mesenteric and coeliac arteries in all patients with pseudocyst. A 10 per cent prevalence of pseudoaneurysm formation[64] justifies this philosophy, especially in patients with chronic pancreatitis. Huizinga and associates[65] also stress the importance of early selective angiography combined with embolization in the management of arterial haemorrhage complicating pseudocysts.

Bleeding appears to be less of a problem after cystojejunostomy[37]. Sankaran and Walt[19] reported a fatal haemorrhage from a suture-line leak in one of 23 patients after cystojejunostomy. Newell and colleagues[62] reported haemorrhage in only one of 59 patients after cystojejunostomy; bleeding resulted from stress gastritis associated with an intra-abdominal abscess.

In a meta-analysis of 1020 patients, the cyst recurrence rate was 2·5 per cent after cystogastrostomy and 4·5 per cent after cystojejunostomy[14]. Recurrence may be due to failure to recognize that a pseudocyst is loculated, failure to drain the most dependent part of the cyst, or failure to provide an adequate cyst–enteric anastomosis. The following case illustrates the problem of non-dependent cyst drainage and an inadequate stoma.

Patient 4. A 57-year-old woman with chronic alcoholic pancreatitis presented with pain from a large pseudocyst, which arose from the head–neck of the pancreas and extended into the right iliac fossa. Cystogastrostomy was performed, but 2 months later the cyst had refilled sufficiently to cause complete gastric outlet obstruction with gross electrolyte derangement. Laparotomy now revealed a 300-ml cyst arising from the neck of the pancreas, extending between the leaves of the lesser omentum and partly surrounding the duodenal cap. On-table cystography showed communication with neither stomach nor pancreatic duct. The cyst was drained by retrocolic Roux-en-Y cystojejunostomy with complete symptomatic relief at 9 months.

Postoperative sepsis is infrequent, occurring in only 2 per cent of patients after internal drainage, but it may contribute to the patient's death[17,62]. Gastrocutaneous fistula is another unusual complication following cystogastrostomy, but it occurred in five of seven patients referred to this tertiary referral centre. The use of stomach to drain the cyst in each case was the direct cause of a gastric fistula to the skin. Although two of these fistulas closed spontaneously, another (patient 3) required several operations culminating in death.

Pseudocyst resection

Resection is an alternative to internal drainage for chronic pseudocysts of moderate proportions, especially those that have largely replaced a portion of the pancreas. Frey[37] performed 26 distal resections and five proximal resections in a series of 131 patients. The indications for resection included painful chronic pancreatitis, multiple cysts, gastrointestinal haemorrhage from pseudoaneurysm, common bile duct obstruction, inability to drain uncinate cysts and duodenal obstruction. Although there was only one operative death in this series, mortality rates of 10 per cent have been reported in association with pseudocyst excision[14,66].

A number of different operations can be used to resect pancreatic pseudocysts. Those in the body and tail are generally treated by distal pancreatectomy with splenectomy[37]. Although we sometimes perform conservative (spleen-preserving) pancreatectomy in chronic pancreatitis, we do not recommend it in patients with pseudocyst because the splenic vessels are generally encased in inflammatory scar tissue and may be compressed or even thrombosed[67]. A desire to minimize the extent of resection in this benign disease has led to the application of pylorus-preserving (and even duodenum-preserving) proximal pancreatectomy for complicated chronic pancreatitis confined to the head of the gland[68,69]. If there is dilatation of the duct in the residual distal pancreas, longitudinal pancreatojejunostomy can be used during reconstruction. A cyst in the head of the pancreas can compress the superior mesenteric or portal vein, with a risk of vascular injury during its removal[70]. Thus visceral angiography is highly desirable before undertaking cyst resection in chronic pancreatitis.

Conclusions

Pancreatic pseudocysts remain a challenging problem in pancreatitis. We agree with D'Egidio and Schein[21,53] that it is important to try to differentiate between acute, acute-on-chronic and chronic pseudocysts to determine the best management plan. Warshaw[71] has commented that new techniques not only facilitate precise diagnosis but also permit modification of the approach to treatment in each case. An algorithm outlining the steps in the management of a pancreatic pseudocyst is proposed (*Figure 1*). Ultrasonography will establish the presence of a pseudocyst, and its age can be estimated from the clinical history and CT findings[46].

Chronic pseudocysts are unlikely to resolve spontaneously. As the risk of a serious complication increases with time, larger pseudocysts (>4–6 cm) should be treated as soon as the diagnosis is made. Smaller asymptomatic chronic pseudocysts can be kept under observation. There is a <10 per cent risk of developing a life-threatening complication in this group[72]. ERCP and angiography should be undertaken before definitive therapy. By contrast, acute peripancreatic collections will often resolve spontaneously so, providing the patient is asymptomatic, an initial 6-week period of observation is justified. Thereafter, small cysts (<6 cm) can be observed safely but larger lesions should be treated by internal drainage. Acute cysts that become symptomatic or enlarge during the initial period of observation require external drainage, ideally by non-operative means.

Pancreatic pseudocysts have traditionally been managed operatively by surgeons. The results of such treatment have been good, with low morbidity and mortality rates[14]. Interventional radiologists and endoscopists have now entered this surgical preserve, but at present there is little evidence that either percutaneous or endoscopic drainage is superior to operative internal drainage. A recent study by Szentes and colleagues[73] compared the various techniques in 59 patients. Invasive non-operative drainage in 25 patients, either radiological or endoscopic, was successful in 92 per cent but carried a mortality rate of 8 per cent and a morbidity rate of 20 per cent. Non-operative drainage plus operation in 22 patients was successful in 82 per cent with mortality and morbidity rates of 5 and 20 per cent respectively; the combined treatment was required mostly for failure or complications of non-operative drainage. Operation alone in 14 patients was successful in 83 per cent with a morbidity rate of 24 per cent and with no death. Similarly, Adams and Anderson[74] recently compared experience of CT-directed percutaneous catheter drainage in 52 patients and operative internal drainage in 42 for management of pseudocysts of mixed aetiology. Operative internal drainage, generally cystogastrostomy, was associated with more (17 per cent; P not significant) major complications and a significantly higher mortality rate (7 *versus* 0 per cent) than percutaneous drainage. However, disadvantages of percutaneous drainage included a prolonged external pancreatic fistula lasting for a mean of 42 days and a drain-track infection rate of almost 50 per cent.

Szentes *et al.*[73] recognized a subgroup of patients with idiopathic fluid collections (i.e. in the absence of gallstones or alcoholism) in whom non-operative drainage proved beneficial. In children at least, percutaneous external drainage may be an appropriate first-line therapy for persisting pseudocysts[75]. A potential advantage of operative drainage in postnecrotic pseudocysts is its ability to clear the solid debris frequently present within the cavity. We believe that the operation of choice for a mature pseudocyst is internal drainage with a Roux loop of jejunum[23]. If a non-operative technique is used, it is important to exclude cystic neoplasms or other lesions masquerading as a pseudocyst[76,77]; failure to improve rapidly should be addressed by formal surgical exploration[78].

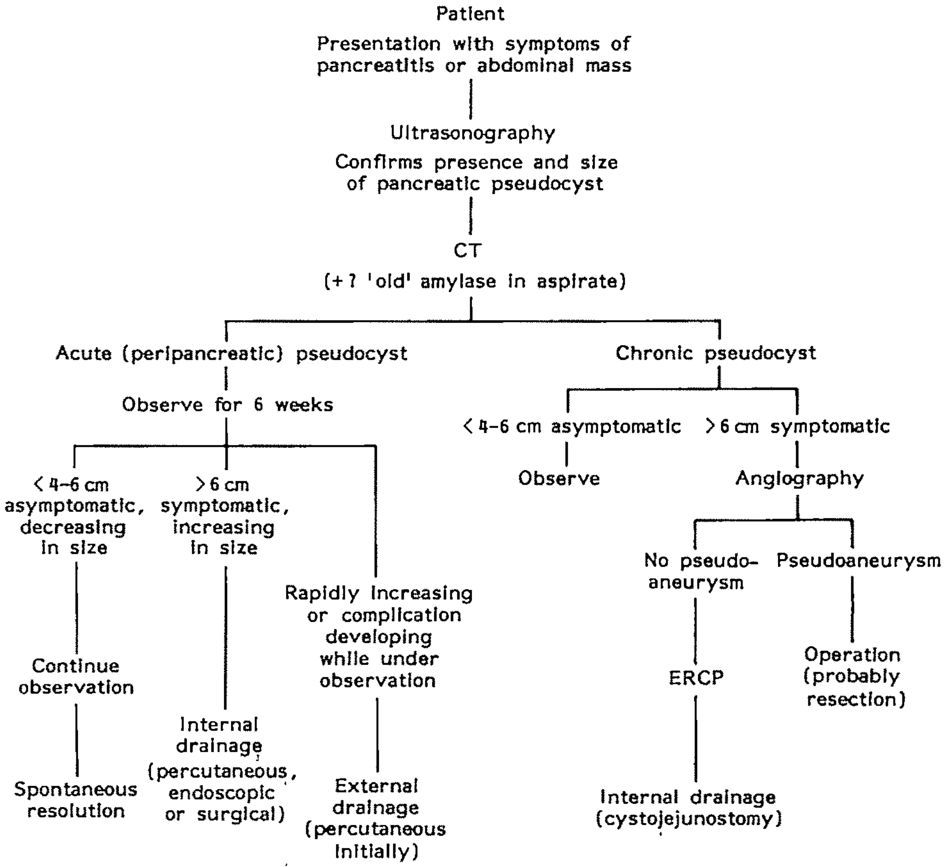
Patient
Presentation with symptoms of pancreatitis or abdominal mass
Ultrasonography
Confirms presence and size of pancreatic pseudocyst
CT
(+? 'old' amylase in aspirate)
Acute (peripancreatic) pseudocyst
Observe for 6 weeks
< 4–6 cm asymptomatic, decreasing in size
Continue observation
Spontaneous resolution
> 6 cm symptomatic, increasing in size
Internal drainage (percutaneous, endoscopic or surgical)
Rapidly increasing or complication developing while under observation
External drainage (percutaneous initially)
Chronic pseudocyst
< 4–6 cm asymptomatic
Observe
> 6 cm symptomatic
Angiography
No pseudo-aneurysm
ERCP
Internal drainage (cystojejunostomy)
Pseudoaneurysm
Operation (probably resection)

Figure 1 *Algorithm for the management of a patient with pancreatic pseudocyst. CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography*

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Announcement

Surgery of the Liver, Biliary System and Pancreas

The British Council are holding a course devoted to Surgery of the Liver, Biliary System and Pancreas in The Royal College of Surgeons of Edinburgh from 17 to 23 October 1993. The course is intended for discussion of complex issues with an audience composed of relatively senior specialist surgeons. Topics to be covered will include: cholelithiasis and choledocholithiasis; minimally invasive hepatobiliary surgery; transplantation of liver and pancreas; acute and chronic pancreatitis; pancreatic and periampullary cancer; hepatobiliary trauma; portal hypertension; and hepatic and biliary malignancy. The course will be directed by Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh.

Further information can be obtained from: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK.

D. C. Carter

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High prevalence of unsuspected abdominal aortic aneurysm in patients with confirmed symptomatic peripheral or cerebral arterial disease

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A group of 561 consecutive patients with proven symptomatic peripheral or cerebral arterial disease attending a vascular clinic was screened for abdominal aortic aneurysm (AAA) using B-mode ultrasonography. An aneurysm was present in 40 of 358 men (11·2 per cent) and 13 of 203 women (6·4 per cent), a total prevalence of 9·4 per cent. Thirty-three aneurysms were 3–4 cm in diameter. The prevalence of AAA was similar in patients referred with lower-limb and with cerebral ischaemia. Physical examination for AAA was performed in 200 patients before ultrasonography. The sensitivity of physical examination in the detection of aneurysm was 43 per cent (57 per cent for AAA ≥4 cm in diameter, 29 per cent for AAA <4 cm in diameter). Physical examination was an inadequate method of screening. Initial follow-up showed a mean aneurysm expansion rate of 0·20 cm/year. Patients with arterial disease have a high risk of AAA; routine ultrasonographic screening should be considered.

Abdominal aortic aneurysm (AAA) is an increasingly common condition[1–5]. Rupture carries an overall mortality rate of 84–94 per cent and many patients die before reaching hospital[6,7]. In contrast, the mortality rate for elective repair in many centres is <5 per cent[8–10]. As rupture is frequently the presenting feature of AAA, screening programmes have been advocated to detect asymptomatic aneurysms to allow elective repair[11].

This study was undertaken to determine the prevalence and size distribution of AAA in defined groups of patients with arterial disease, to compare physical examination with B-mode ultrasonography as a screening technique, to determine whether the prevalence of AAA differed according to presenting symptoms, and to measure the rate of growth of detected aneurysms.

Patients and methods

Of 561 consecutive outpatients with arterial disease, 456 were referred with symptoms of lower-limb ischaemia (claudication, rest pain or gangrene) and 105 with symptoms of cerebrovascular insufficiency (stroke, transient ischaemic attack or amaurosis fugax). Individuals referred because of known or suspected AAA or who had undergone previous aortic surgery were excluded.

Patients presenting with symptoms suggesting lower-limb ischaemia underwent Doppler measurement of the systolic ankle:brachial pressure index (ABPI) and a 1-min exercise test[12]. A positive diagnosis was made if the resting ABPI was <0·9 or if there was a fall in ankle pressure after exercise testing >30 mmHg from the resting level[12].

The opinion of a neurologist was sought if patients presented with symptoms suggesting cerebrovascular disease, and carotid duplex scanning was undertaken. Only if the neurological opinion supported the diagnosis and duplex scanning showed carotid artery stenosis ≥25 per cent on the appropriate side was the patient included in the study.

All patients underwent measurement of the aortic diameter using a 4·0-MHz ultrasonographic probe (Sonolayer SAL32B; Toshiba, Crawley, UK). A maximum external anteroposterior diameter ≥3 cm was used to define an aneurysm.

Technique of measurement

The abdominal aorta was first imaged throughout its length to allow the observer to look for areas of dilatation and to determine its lie and tortuosity. This enabled the ultrasonographic probe to be positioned at 90° to the long axis of the aorta, thus measuring the true cross-sectional rather than the oblique diameter. Any dilatation was imaged at its maximum anteroposterior extent. When the optimal image was obtained it was frozen at the moment of maximum diameter to minimize error caused by aortic pulsation. The external anteroposterior diameter was then measured. This process was repeated twice and the diameter expressed as the mean of the three measurements.

An unselected series of 200 of these patients underwent physical examination before ultrasonography to determine the sensitivity and specificity of such examination as a screening technique. As clinical examination is known to be an inaccurate means of sizing aneurysms, no attempt was made to do this[13–16]. Instead, each patient was examined by one of the authors and the aortic palpation graded as normal or aneurysmal (or the aorta was impalpable) before ultrasonography was performed.

Results

An aneurysm was present in 40 of the 358 men (11·2 per cent) and 13 of the 203 women (6·4 per cent), a total prevalence of 9·4 per cent. The prevalence of AAA in patients presenting with lower-limb ischaemia (42 of 456; 9·2 per cent) was similar to that in those with cerebrovascular disease (11 of 105; 10·5 per cent). The size distribution of AAAs in men and women is shown in *Figure 1*. Many aneurysms detected (33 of 53; 62 per cent) were <4 cm in size, the median diameter being 3·7 (range 3·0–6·1) cm. The sensitivity and specificity of physical examination in the detection of AAA are shown in *Figure 2*. The overall sensitivity of physical examination was 43 per cent. This increased to 57 per cent in patients with AAAs ≥4 cm in diameter and was 29 per cent in those with aneurysms <4 cm in size. The aorta was impalpable in 35 of the 200 patients (17·5 per cent).

Preliminary data on the growth rate of AAAs detected by screening are available for 38 of the 53 patients. Four underwent elective repair on detection, three died, one refused follow-up and seven have not yet had a repeat scan. The mean growth rate was 0·20 (range −0·2 to 0·7) cm/year. The mean growth rate for AAAs ≥4 cm in size was 0·27 cm/year, compared with 0·15 cm/year for those <4 cm (P not significant). The mean duration of follow-up was 16 (range 12–24) months.

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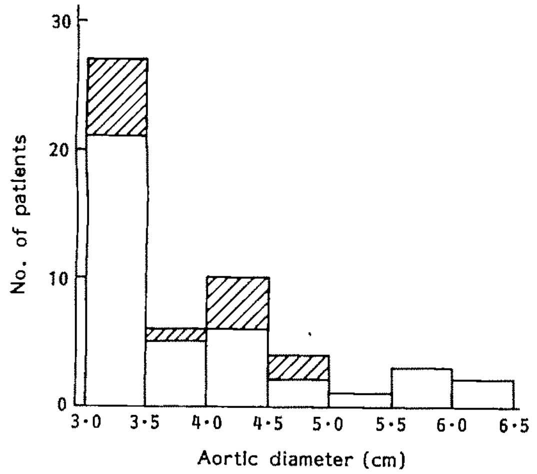

Figure 1 *Size distribution of aneurysms detected by ultrasonography in men* (☐) *and women* (■)

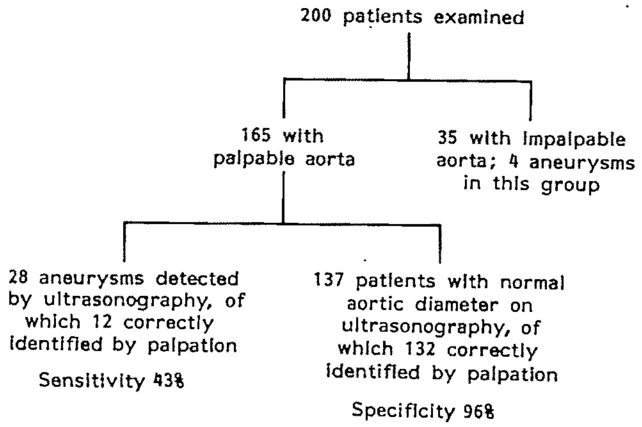
200 patients examined
165 with palpable aorta
35 with impalpable aorta; 4 aneurysms in this group
28 aneurysms detected by ultrasonography, of which 12 correctly identified by palpation
Sensitivity 43%
137 patients with normal aortic diameter on ultrasonography, of which 132 correctly identified by palpation
Specificity 96%

Figure 2 *Sensitivity and specificity of physical examination in screening for asymptomatic aneurysm*

Of the 53 patients with AAA identified, four underwent early elective repair and, to date, two have had subsequent elective repair because of an increase in aneurysm size.

Discussion

The results of this study confirm that patients with arterial disease are at high risk of AAA and are consistent with data from previous smaller series. Allardice *et al.*[17] screened 100 patients with arterial disease (75 men, 25 women) of whom 95 per cent presented with lower-limb ischaemia, 2 per cent with transient ischaemic attack and 3 per cent with 'other' aneurysms. An AAA was present in 14 per cent of men and 4 per cent of women, compared with 3 per cent and none respectively in a control group with bronchogenic carcinoma. Bengtsson *et al.*[18,19] found an aneurysm in 12·0 per cent of patients who had undergone previous carotid endarterectomy and 11·8 per cent of those with intermittent claudication. Cabellon and colleagues[20] reported that the prevalence of AAA was 11 per cent in 63 patients who presented with transient ischaemic attack and zero in seven with lower-limb ischaemia. Shapira *et al.*[21] screened 101 patients, of whom 65 presented with lower-limb ischaemia and 36 with transient ischaemic attack, and found AAA in 6 per cent. From post-mortem studies[22,23], the expected prevalence in the population is between 1·8 and 2·1 per cent. Community-based population screening programmes[24,25] found aneurysms >3·5 cm in diameter in 2·7 per cent of people aged 65–85 years and 3·4 per cent of men aged 65–79 years.

Comparison between different studies is complicated by the lack of an agreed definition of AAA. Definitions used in the above studies varied between >1·5 times the suprarenal aortic diameter[17], any increase in diameter in the distal aorta, aneurysm 'considered to be present' at post mortem[18,19], not stated[20], a diameter >0·5 cm larger than the proximal aorta or[21] >3·0 cm, >3·0 cm diameter or more than twice the suprarenal diameter[24], and >4·0 cm or >0·5 cm larger than the suprarenal aorta[25]. Ultrasonographic measurement of the suprarenal aortic diameter is poorly reproducible[16]; the most reproducible measurement is the maximum infrarenal diameter measured in the anteroposterior plane[16]. Definition of AAA should refer to this measurement, as in the present paper.

In the present study, palpation was a poor method of detecting AAA, missing over half. Although it might be argued that missing a small (<4 cm) aneurysm is not clinically important, the detection rate for larger lesions (⩾4 cm), which might be considered at risk of rupture, was still only 57 per cent.

Other workers have found clinical examination to be inadequate. In a series of studies in which physical examination was used for screening of AAA, sensitivity ranged from zero to 50 per cent and specificity from 84 to 97 per cent[15,17,25–28]. It is probable that the sensitivity of examination by a surgeon with a vascular interest, looking specifically for AAAs with the knowledge that accuracy will be tested by ultrasonography, is greater than that of 'routine' abdominal examination. It seems likely, therefore, that the detection rate in everyday clinical practice will be worse than the above. Screening by clinical examination is too insensitive to provide an accurate estimate of the prevalence of AAA.

The slow growth rate of AAAs detected by screening is consistent with recent studies of growth rates of small aneurysms[29,30], although there was considerable individual variation. However, earlier studies using serial ultrasonography reported higher mean expansion rates. Bernstein *et al.*[31] found a mean expansion rate of 0·4 cm/year in 110 patients, Cronenwett and colleagues[32] reported growth rates of 0–1·5 cm/year in 67 patients and Littooy *et al.*[33] a mean rate of 0·79 cm/year in 149. It is of interest that, of a total of 326 AAAs examined in these studies, not one underwent an apparent decrease in size. The variability of ultrasonographic measurement of aortic diameter is such that two successive measurements performed minutes apart may vary by an amount equivalent to the mean annual expansion rate[16]. It would, therefore, be expected that at least some AAAs would undergo an apparent decrease in size. If this variability is not recognized, it would be easy to discount an apparent decrease in size as an error and repeat the measurement, so introducing a systematic bias and overestimating mean expansion rate. If accurate data on the rate of growth of AAA are to be obtained, it is important that measurements should not be influenced by previous results.

If further follow-up confirms these preliminary results, frequent rescanning of small AAAs may prove unnecessary. However, until more definitive data become available, patients will continue to be closely monitored by serial ultrasonography. To demonstrate the benefit of a screening programme it is necessary to know the improvement in prognosis that follows earlier detection. Benefit is also related to the resources required, the prevalence of the condition, the screening technique used and the population studied.

Although the large difference in the mortality rate of elective compared with emergency aneurysm repair provides compelling evidence for the benefit of detection before rupture, it is not known how large an AAA must be before the risk of death from rupture outweighs the risk of death from elective repair. Until such data become available, the magnitude of survival benefit as a result of earlier detection of AAA remains uncertain[10]. However, ultrasonography of the abdominal aorta is a straightforward procedure that can easily be learned by an interested clinician. The time required to scan the aorta is comparable to that taken to measure the Doppler ABPI, a routine outpatient procedure. Appropriate patients are readily available to the vascular surgeon and a routine scan of new referrals can be achieved with relatively little additional burden.

The yield will be considerably greater than from community screening programmes and cost less. For comparison, the yield from breast cancer prevalence screening[34] is 7 per 1000. In addition to the detection of large AAAs requiring repair, the finding of an AAA may also influence the choice of revascularization procedure. For example, aortobifemoral bypass might be considered in preference to extra-anatomic reconstruction, allowing an AAA to be repaired at the same procedure.

It is concluded that, as most vascular surgeons repair asymptomatic AAAs considered to be at high risk of rupture, it would seem reasonable in the present state of knowledge to screen all patients presenting with peripheral vascular disease because many have an unsuspected aneurysm. Most patients with small AAAs require careful follow-up and a few with large aneurysms should undergo early repair. Screening should be performed by ultrasonography as physical examination is unreliable. Which of the aneurysms detected by screening are repaired will depend on local policy until the results of future studies become available[35].

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Comparison of long-term survival after successful repair of ruptured and non-ruptured abdominal aortic aneurysm

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Long-term survival was assessed after the repair of non-ruptured (n = 311) and ruptured (n = 227) abdominal aortic aneurysm. Follow-up was 94·2 per cent complete, and the overall survival rate at 8 years was 43·6 per cent. There was no significant difference in 8-year survival rates between patients with non-ruptured (45·2 per cent) and ruptured (40·5 per cent) aneurysms. The survival curves were also compared with that for an age- and sex-matched population derived from Scottish Home and Health Department data.

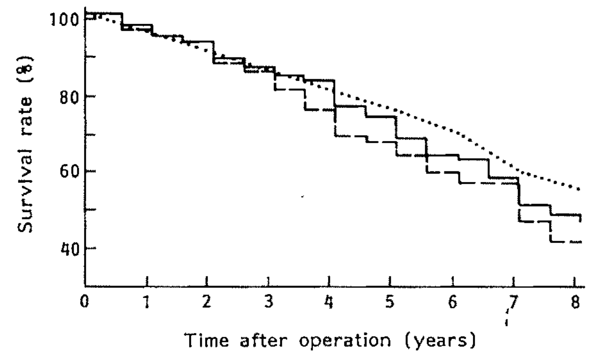
Postoperative mortality rates of patients with ruptured abdominal aortic aneurysm (AAA) vary between 30 and 60 per cent[1,2], with only an estimated 38–64 per cent of patients reaching hospital[3]. The overall mortality rate of patients in the community suffering rupture of an aortic aneurysm has been placed as high as 85–95 per cent[4,5]. Elective surgery is presently associated with operative mortality rates of 2–15 per cent[6,7]. Two questions arise. First, with the rising incidence of AAA and the high cost of repair, do the long-term results justify this type of operation? Second, is there a difference in the long-term survival in these two groups after repair, especially as modern surgical and anaesthetic techniques will possibly allow a better short-term result in higher risk candidates? Experience of 538 aneurysm operations and their long-term outcome has been analysed.

Patients and methods

All patients who underwent AAA repair in this unit over a 10-year period (1980–1989) were reviewed. Information on inpatient morbidity was obtained from case notes and unit statistics were prospectively assembled as part of the Lothian Surgical Audit. Follow-up data were obtained from hospital records and postal questionnaires were sent to general practitioners according to a fixed protocol. The results were analysed using standard life-table methods.

Results

The number of aortic aneurysm repairs carried out in the study period was 538, with an overall hospital mortality rate of 13·6 per cent. Some 227 patients had ruptured aneurysms (operative mortality rate 26·8 per cent), with a mean age of 71 years and a male:female ratio of 5:1. There were 311 cases of non-ruptured aneurysm, including acute symptomatic, elective symptomatic and elective asymptomatic cases (operative mortality rate 3·8 per cent); these patients had a mean age of 68 years and a male:female ratio of 4:1. Of the 465 postoperative survivors, long-term survival was assessed in 94·2 per cent; 27 were lost to follow-up for a variety of reasons. The overall 8-year survival rate after aortic aneurysm repair was 43·6 per cent. This figure is compared with an age- and sex-matched normal population based on Scottish Home and Health Department data (*Figure 1*). A total of 45·2 per cent of patients with non-ruptured aneurysms and 40·5 per cent of those with ruptured aneurysms were alive and well 8 years after operation. There was no significant difference between the two groups after operation.



	1	2	3	4	5	6	7	8
No. at risk								
Non-ruptured	248	203	159	110	74	41	27	19
Ruptured	138	101	82	49	31	16	10	4
95% c.i. of combined survival rate (%)	91·2–95·8	84·2–90·8	78·5–86·3	68·0–78·0	59·5–71·4	52·5–66·1	39·4–56·7	34·2–51·1

Figure 1 *Life-table analysis of survival after successful repair of non-ruptured (——) and ruptured (——) aortic aneurysm, compared with that of an age- and sex-matched normal population (·····). c.i., Confidence interval*

Discussion

There are conflicting data about the life expectancy of patients with proven aortic aneurysms who do not undergo operative repair. Estes[8] reported an overall 5-year survival rate of 19 per cent. In the series of Szilagyi *et al.*[9] of patients deemed unfit for operation, 43 per cent with aneurysms >6 cm in diameter and 31 per cent with aneurysms <6 cm had succumbed to a ruptured aneurysm within 2 years. The rupture rate, however, has been reported[10] to be as low as 8 per cent at 10 years in a population-based study using ultrasonography. Despite the doubt about the true mortality rate of AAA, the overall elective mortality rate (asymptomatic and symptomatic aneurysms) in the present series was 1·9 per cent; this figure supports elective repair.

There is no significant difference in survival between the two postoperative groups (ruptured and non-ruptured). Furthermore, if the age difference between the two groups is taken into account, any survival effect is virtually eliminated. Although the long-term survival of an age- and sex-matched normal population does not fall outside the 95 per cent confidence interval of either group, there is a fall-off of the survival curve

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with increasing time or age of the patient, implying that other factors associated with either disease or operation also have an effect on long-term outcome. Angiography studies have shown a 47–65 per cent incidence of coronary artery disease in the aneurysm population[11]. Patients without hypertension or ischaemic heart disease are reported to have survival equivalent to that of an age- and sex-matched population, with acute myocardial infarction and other complications of coronary artery disease being responsible for 38–70 per cent of all late deaths[12,13]. White and colleagues[14] showed that poor cardiac risk status (Goldman index 3–4), cerebrovascular disease or deteriorating renal function, either singly or in combination, adversely affect long-term survival. Conversely, the long-term survival of patients with ruptured AAA has been improved because of selection through 'trial by repair', i.e. those with pre-existing coronary artery disease and poor Goldman index are not surviving the trauma of rupture and operation, and are therefore not contributing negatively to the survival curve.

During the 8-year follow-up of the 154 deaths, 18 (11·7 per cent) were reported to be from malignant disease, the same percentage as that given by the Scottish Home and Health Services for death from cancer among all individuals over 55 years of age. Twelve patients (7·8 per cent) died following a cerebrovascular accident, compared with an 11 per cent incidence in the Scottish population. The long-term survival of the present population is comparable to that of the 1981 series[15] from the UK of comparable size and, more recently, that of series from the USA[12,13]. The quality of life in such patients is comparable to that of a matched population[16].

The encouraging long-term outlook after AAA repair combined with the low mortality rate of elective operation suggests a policy of screening at-risk populations, despite the economic implications. Once the repair has been successfully performed for ruptured or non-ruptured aortic aneurysm, patients can be reassured that their survival is not significantly different from that of the normal population.

Acknowledgements

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Mesothelial seeding of knitted Dacron

Bilateral superficial femoral artery replacement using knitted Dacron was performed in 38 dogs. One side was seeded with omental mesothelium and the other acted as an unseeded control. ^{111}*In-labelled platelet accumulation on grafts was measured at 5 days and 2 months and the thrombogenicity index of seeded and unseeded grafts calculated. Patency was monitored for 2 months, at which time grafts were removed and luminal thrombus, ultrastructural cell cover and prostacyclin release were measured. Cell seeding did not influence the mean(s.e.m.) thrombogenicity index of 0·95(0·25) and 0·88(0·24) at 5 days in control and seeded grafts respectively; nor was there any difference between the groups at 2 months. Occlusion occurred in six control and four seeded grafts. Seeding did not significantly improve the percentage thrombus-free area or luminal cell cover. Neither did it enhance mean(s.e.m.) luminal 6-keto-prostaglandin* $F_{1\alpha}$ *release of 2·58(0·80) pg cm*$^{-2}$ *in controls and 2·63(0·78) pg cm*$^{-2}$ *in seeded grafts. Further studies demonstrated that only a mean(s.e.m.) of 4·4(1·9) per cent of the seeded inoculum was present on grafts 48 h after implantation, providing too few cells to achieve confluent cover. Mesothelial cell seeding might be useful in promoting a healed graft surface but critical levels of seeding density must be achieved before the technique can be properly evaluated.*

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The prosthetic grafts currently used for arterial bypass are thrombogenic, leading to platelet deposition on contact with flowing blood and thrombosis in small-artery bypass[1]. These grafts remain thrombogenic because they fail to re-endothelialize in humans, and chronic platelet deposition leads to graft occlusion by neointimal hyperplasia or thrombosis[2,3]. Endothelial cell seeding may promote graft endothelialization experimentally; it has accelerated maturation, enhanced thromboresistance and increased patency[4]. Similar results have not been reported in clinical trials where cell availability, retention and proliferation after graft implantation are problematic[4,5].

Mesothelial cells possess similar antithrombotic and fibrinolytic activity and proliferate to confluence *in vitro*[6]. Omentally derived cells have been successfully seeded on to knitted Dacron (Meadox (UK), Caddington, UK) implanted in the canine aorta. By 6 weeks, seeded grafts developed areas of confluent luminal cover, inhibiting platelet deposition and improving prostacyclin production, compared with unseeded controls[7,8].

The canine aorta model relates to large-artery bypass, but the problem of prosthetic graft thrombosis affects grafts that bypass smaller arteries. Mesothelial cell seeding was, therefore, re-evaluated in a canine model of small-artery bypass. The influence of seeding on graft thrombogenicity, maturation, prostacyclin release and patency was studied initially; the failure of seeding to improve these factors led to an investigation of the efficiency of the seeding technique.

Materials and methods

Mesothelial cell seeding was performed on one side (randomized) of bilateral femoral artery replacement by knitted Dacron in 38 female greyhounds weighing 25–30 kg. Cell harvesting, seeding and graft implantation were carried out under a single general anaesthetic. Cefuroxime (500 mg) was given intravenously on induction and at 12 h as antibiotic prophylaxis. A minilaparotomy was performed to obtain 20 g omentum, which was incubated in 0·3 per cent collagenase (Boehringer Mannheim, Livingston, UK) at 37°C for 20 min. The resulting cell suspension (10^5–10^6 cells ml^{-1}) was washed three times by centrifugation and resuspended in 5 ml phosphate-buffered saline (PBS). Cell viability was checked by adding trypan blue dye (1:10 (v/v)) to an aliquot of cell suspension and counting the percentage of stained cells 5 min later. Assessment of cell numbers in the seeding inoculum, which is difficult because mesothelial cells remain in sheets, was carried out using a haemocytometer (Webb Scientific International, London, UK).

Knitted Dacron, 6 cm long × 6 mm in diameter (Microvel; Meadox (UK)), was preclotted in three stages of 10 ml venous blood followed by a further 10 ml containing 10000 units heparin[9]. Mesothelial cells were incorporated by random code during the first and second stages by adding 2-ml aliquots of cell suspension to 8 ml venous blood (*Figure 1*).

The superficial femoral artery was fully exposed along its length and the profunda femoris ligated to prevent collateral formation. The superficial femoral artery was divided and a 4-cm segment removed. The cut ends retracted, permitting the implantation of a 6-cm length of Dacron anastomosed end to end using 6/0 polypropylene.

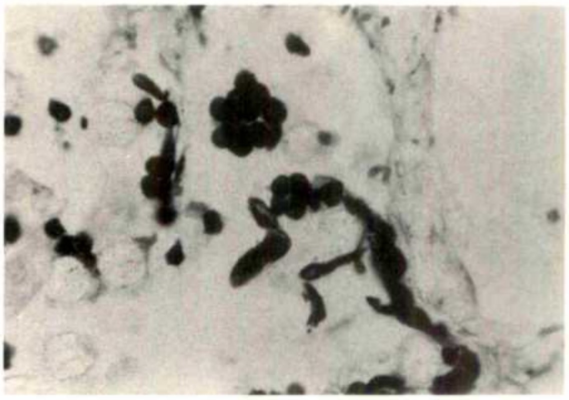

Figure 1 *Knitted Dacron freshly seeded with mesothelial cells released from omentum by collagenase. Seeded cells are within the graft interstices and stained with the antipancytokeratin monoclonal antibody MNF116. (Light micrograph, original magnification × 360)*

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Measurement of thrombogenicity

Graft thrombogenicity was measured by recording the accumulation of autologous ^{111}In-labelled platelets on seeded and control grafts. A standard technique was used to label autologous platelets with ^{111}indium oxine (Amersham International, Amersham, UK)[10]. At 5 days and 2 months after surgery, graft ^{111}In-labelled platelet deposition was measured over 6 days using a 50 × 50 mm thallium-activated sodium iodide crystal probe detector collimated to exclude radiation from the liver and spleen. The probe detector was connected to a single-channel ratemeter peaked to the 249-keV energy peak of ^{111}In (Nuclear Enterprises SAM1, N. E. Technology, Reading, UK). The position of the animal and the site of recording were standardized to ensure consistent probe geometry. A 5-ml venous blood sample was taken at the same time and emission counted using the same probe. Both grafts and whole blood radioactivity were corrected for background. The rate of platelet accumulation on the implanted Dacron, expressed as the thrombogenicity index, was recorded as the daily rise in the ratio of graft activity divided by whole blood activity and calculated using linear regression analysis[11].

Measurement of luminal prostacyclin release

Release of 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-PGF$_{1\alpha}$) was measured from the flow surface of excised grafts and from the femoral artery proximally. A 0·5-cm^2 section of graft 1·2 and 2·4 cm from the proximal anastomosis was exposed to 0·9 ml of 1 μmol l^{-1} calcium ionophore A23187 (Sigma Chemicals, Poole, UK) in PBS in a specially constructed block. After 20 min 100 μl was removed, diluted 1 in 5 with PBS and analysed for 6-keto-PGF$_{1\alpha}$, the stable metabolite of prostacyclin, using a radioimmunoassay[8,12].

Measurement of thrombus-free area

At 2 months the animals were reanaesthetized, 20000 units heparin administered, the grafts removed, and the animal killed by intravenous injection of sodium pentobarbitone.

The excised grafts were flushed with 5 ml PBS at 37°C and opened longitudinally, photographed and the colour transparency projected on to a digitizer pad (Kontron MOP system, London, UK). Images were examined independently by two observers. The proportion of graft luminal surface covered, free from red thrombus, was calculated as thrombus-free area[13].

Immunohistochemistry

Seven pairs of seeded and control grafts removed at 2 months were chosen by random number. Specimens were fixed immediately in formol saline and embedded in paraffin wax. Grafts were sectioned transversely at the mid-graft and longitudinally at the anastomoses. Adjacent sections were taken for haematoxylin and eosin staining and immunohistochemistry.

Mesothelial cells on paraffin sections can be identified using a murine antihuman cytokeratin monoclonal antibody, DAKO-CK (clone MNF116) (Dako, High Wycombe, UK). This antibody reacts with a variety of human epithelial tissue and recognizes an epitope expressed on a broad range of cytokeratins, including 17 and 18, which are expressed by mesothelial cells[14]. Sections were also stained with AuA1 (Imperial Cancer Research Fund, London, UK), a murine antihuman monoclonal antibody that reacts with tumours of epithelial origin and is used to distinguish carcinoma from mesothelioma in cases of pleural effusion. The epitope with which it reacts is unknown but in human tissue it does not stain mesothelial cells. Specimens were also stained with a rabbit anti-von Willebrand's factor polyclonal antibody to identify endothelial cells (gift from Dr D. Dodds, New York State Health Department, Albany, New York, USA). Antibodies were tested against control sections of canine artery, small bowel and peritoneum. MNF116 stained mesothelium and epithelium, the anti-von Willebrand's factor antibody stained canine endothelial cells, while AuA1 failed to stain any tissue and acted as the negative control.

Sections were placed in an oven at 56°C for 12–18 h, then dewaxed and rehydrated. Endogenous peroxidase activity was inhibited by incubating sections with 0·5 per cent hydrogen peroxide in methanol for 10–15 min before washing in running water for 5 min. All specimens were treated with trypsin for 5–10 min using freshly prepared enzyme, washed with cold tap-water and then twice with tris-buffered saline (TBS) for 5 min. Non-specific binding of protein was blocked by incubating sections with normal rabbit serum (Dako) diluted 1 in 5 with TBS for 10 min. The primary antibody was then applied and after 30 min the slides were rinsed in TBS. Either biotinylated swine antirabbit serum or rabbit antimouse serum with normal human serum was applied for 30 min and the sections rinsed with TBS. Avidin–biotin complex horseradish peroxidase (Dako) was applied for 30 min and sections then treated with diaminobenzidine solution for 10 min. After washing with TBS and running water, and counterstaining with Mayer's haematoxylin, the sections were dehydrated and mounted using Canadian balsam and a glass coverslip. A positive result demonstrated peroxidase brown. Sections were examined blind by two independent observers.

Scanning electron microscopy

Longitudinal strips (6 cm × 2 mm) of the excised graft were divided into proximal anastomotic, mid-graft and distal anastomotic segments, washed in cacodylate buffer at pH 7·2 and fixed in 1 per cent (w/v) osmium tetroxide in a fresh solution of the same buffer for 1 h. Specimens were washed in distilled water, dehydrated through a graded alcohol series and then transferred to trichlorotrifluoroethane from which they were critical point dried using carbon dioxide as the transitional fluid. Specimens were mounted on stubs using silver conductive paint. After coating with gold in a sputter coater (Polaron, London, UK) they were examined in a JEOL JSM35 scanning electron microscope (JEOL, Tokyo, Japan). In total, 40 mm^2 of each graft was examined at low (× 10) and high (× 600) power. Planimetric assessment of luminal cell cover was carried out using micrographs of the whole specimen taken at low power. High-power electron micrographs were used to verify the presence of endothelium or endothelium-like cell cover and to identify areas of platelet adhesion and aggregation. An x–y digitizer was used to calculate the percentage of luminal cell cover (Kontron MOP system).

Mesothelial cell radiolabelling

^{111}Indium oxine has been used to radiolabel platelets, leucocytes and endothelial cells for cell kinetic studies without effects on cell function, at least for 24 h. The study period can be extended for up to 1 week because the isotope has a half-life[15–17] of 67·4 h.

Mesothelial cells harvested from seven dogs were radiolabelled by incubation with 200 μCi ^{111}indium oxine in tris buffer (Amersham International) for 2·5 min at 24°C. Cells were then centrifuged and washed with medium 199 (Gibco, Paisley, UK) to remove unbound radioactivity, and finally resuspended in 5 ml PBS. The efficiency and activity of the labelling procedure were calculated by counting samples of the cell suspension and discarded supernatant in a well crystal connected to a ratemeter. Dosage was calculated by comparing the radioactivity with that of a known standard. The mean(s.e.m.) efficiency of mesothelial cell radiolabelling was 91·7(2·8) per cent with a mean(s.e.m.) dose of 152(45) μCi. Cell viability was always >90 per cent.

Measurement of seeding efficiency and cell retention

The radiolabelled seeding inoculum was incorporated during the first and second stages of the four-stage preclotting procedure in seven animals. At each stage, graft radioactivity was measured using the sodium iodide crystal probe detector with the ratemeter peaked to the 249-keV energy peak of ^{111}In. The seeding efficiency at each stage was expressed as a percentage of the radioactivity in the seeding inoculum.

After implantation, graft radioactivity was measured at release of clamps and every 5 min up to 30 min after graft implantation. The animal was then placed under a wide field of view γ camera (Aura Scientific, Livingston, UK) fitted with a medium-energy collimator set to record graft radioactivity at 45 min and then at 24 and 48 h. A computer program was used to calculate the radioactivity emitted from selected 'regions of interest' and daily values for graft regional radioactivity and local tissue background were obtained. True graft radioactivity was obtained by subtracting local tissue background from graft regional radioactivity. All counts were corrected for radioactive decay using 67·4 h as the half-life of ^{111}In.

Retention up to 48 h was calculated as a percentage of the harvest inoculum. Release of inoculum into the circulation was monitored by measuring the radioactivity in 5 ml whole blood at 30 min and at 24 and 48 h.

Statistical analysis

Measurements from seeded and unseeded grafts were compared using the Wilcoxon matched pairs signed rank test for non-parametric paired data. The Mann–Whitney U test was used to compare graft and arterial release of 6-keto-PGF$_{1\alpha}$. Log rank survival analysis was used to compare patency of seeded and unseeded grafts. The percentage cell retention data, expressed as the mean(s.e.m.), at seeding and after graft implantation were subjected to analysis of variance.

Results

Two dogs died during anaesthesia. Six of the remaining 36 animals had to be killed to avoid suffering during the study

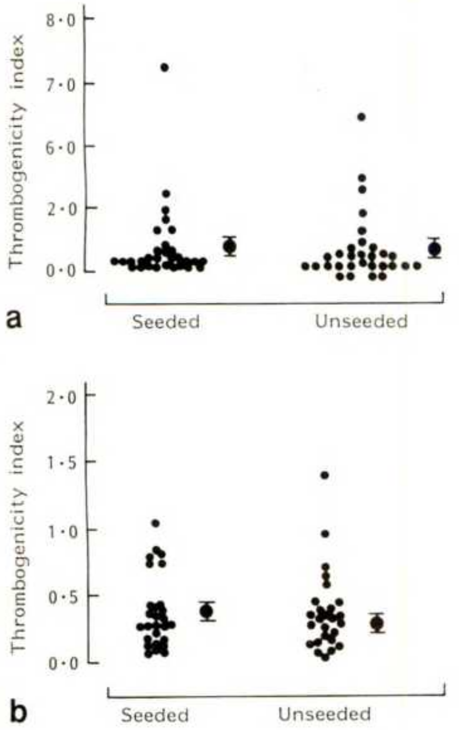

Figure 2 *Thrombogenicity index in seeded and unseeded grafts. Bars are mean(s.e.m.) values. Grafts at* **a** *5 days and* **b** *2 months after surgery.* P *not significant (Wilcoxon signed rank test)*

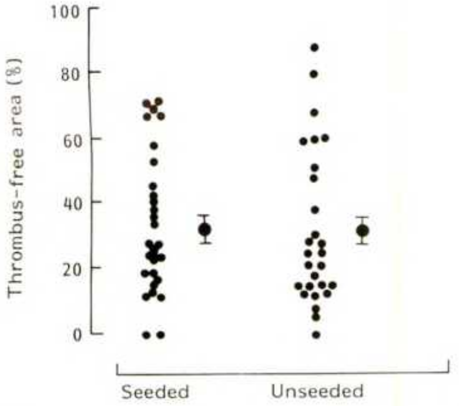

Figure 3 *Luminal thrombus-free area in seeded and unseeded grafts. Bars are mean(s.e.m.) values.* P *not significant (Wilcoxon signed rank test)*

period: two from secondary graft haemorrhage at days 7 and 8 (both seeded grafts), one from infection at day 10 (unseeded) and three from graft occlusion between days 3 and 6 (one unseeded, two bilateral). By 2 months, late but asymptomatic occlusion had occurred in a further four dogs (one seeded graft, two unseeded, one bilateral). Graft occlusion, haemorrhage or infection therefore occurred in six of 36 seeded and seven of 36 unseeded grafts. Seven female greyhounds received a Dacron femoral graft seeded with radiolabelled inoculum and an unseeded control. One died under anaesthetic. All other grafts remained patent at 2 months.

Graft thrombogenicity

The mean(s.e.m.) graft thrombogenicity index at 5 days was 0·95(0·25) in unseeded grafts and was not significantly altered by seeding at 0·88(0·24) (*Figure 2a*). At 2 months, when previous studies indicated good luminal healing, the mean(s.e.m.) index was 0·38(0·08) in unseeded and 0·47(0·08) in seeded grafts (*P* not significant) (*Figure 2b*).

Luminal prostacyclin release

Control mean(s.e.m.) graft release of 6-keto-PGF$_{1\alpha}$ was 2·58(0·80) pg cm^{-2} compared with 2·63(0·78) pg cm^{-2} in seeded grafts (*P* not significant). Release of 6-keto-PGF$_{1\alpha}$ from grafts was markedly less than from the proximal femoral artery at a mean(s.e.m.) of 47·0(11·3) pg cm^{-2} ($P < 0·001$).

Thrombus-free area

Similarly there was no significant effect on deposition of thrombus on the luminal surface of the grafts removed 2 months after implantation. The mean(s.e.m.) thrombus-free area was 30·8(4·7) per cent in controls and 32·5(4·0) per cent in seeded grafts (*Figure 3*).

Immunohistochemistry

In both seeded and control grafts, anastomotic incorporation was by pannus ingrowth from the host artery. This was covered by endothelium, characteristically staining positively with anti-von Willebrand's factor antibody but not with MNF116 or AuA1. In three seeded and two unseeded grafts, macrophages within the perianastomotic thrombus were stained by MNF116 but not anti-von Willebrand's factor antibody or AuA1. At the mid-graft of both seeded and control grafts, the neointima was thin and less cellular than in the region of perianastomotic incorporation. There were no cells that stained positively with MNF116 on the flow surface or within the interstices. Where the luminal surface was covered by flattened cells, these stained with the anti-von Willebrand's factor polyclonal antibody.

Scanning electron microscopy

Low-power micrographs of the perianastomotic regions of seeded and control grafts demonstrated a pannus ingrowth of

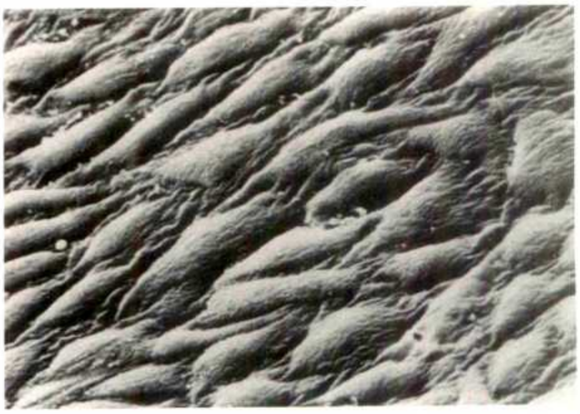

Figure 4 *Luminal surface of perianastomotic pannus tissue proliferating over the graft. This is covered by cells with the cobblestone appearance typical of endothelium. (Original magnification × 900)*

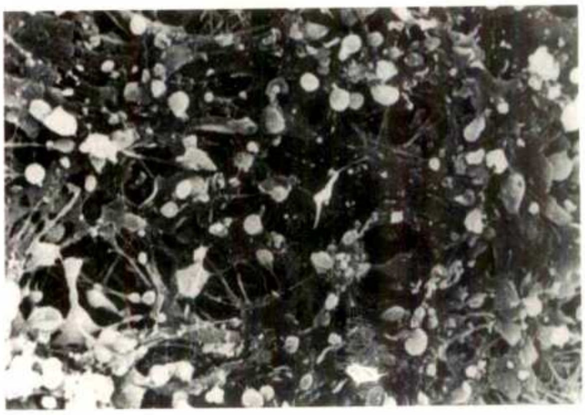

Figure 5 *Luminal surface of a seeded graft explanted at 2 months. No luminal cell cover is present in this field and the graft is covered by thrombus. (Original magnification × 900)*

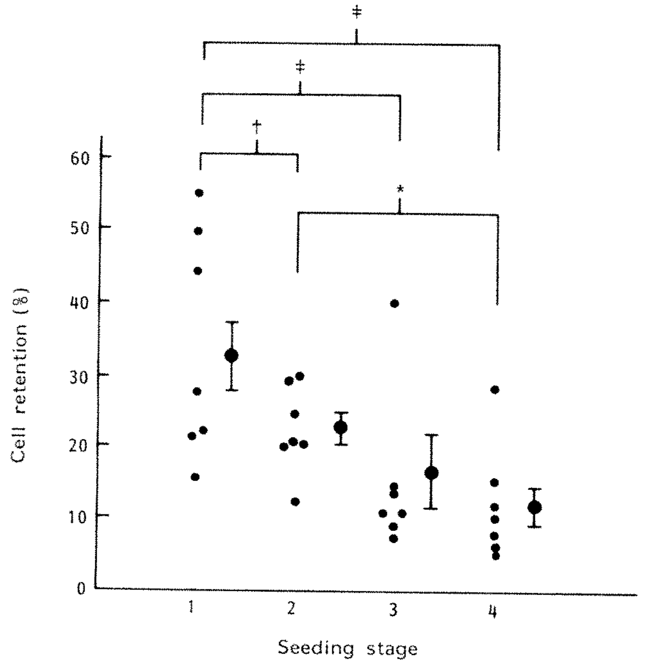

Figure 6 *Retention of ^{111}In-labelled mesothelial cells during preclotting stages 1–4 of knitted Dacron. Mesothelial cells were seeded during stages 1 and 2. Bars are mean(s.e.m.) values.* *$P < 0{\cdot}05$; †$P < 0{\cdot}01$; ‡$P < 0{\cdot}001$ (*analysis of variance*)

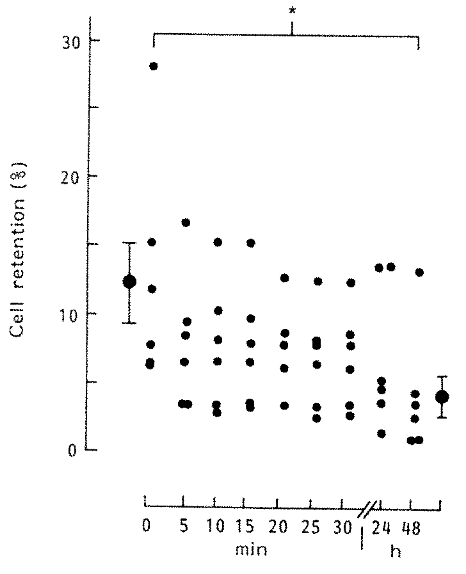

Figure 7 *Retention of ^{111}In-labelled mesothelial cells on Dacron femoral grafts up to 48 h after surgery. Bars are mean(s.e.m.) values.* *$P < 0{\cdot}05$ (*analysis of variance*)

arterial tissue across the anastomoses. High-power views confirmed that the luminal surface was covered by endothelium. Mid-graft sections of both seeded and control grafts demonstrated subconfluent and absent cell cover. When present, luminal cell cover was similar in morphology to the perianastomotic endothelium and derived from transmural capillary ingrowth. The mean(s.e.m.) luminal cover by endothelium was 48·2(8·8) per cent in control and 56·4(8·9) per cent in seeded grafts (P not significant) (*Figures 4* and *5*).

Inoculum retention at seeding

The initial mean(s.e.m.) adherence of seeded inoculum was 33·7(6·0) per cent but, after the second aliquot of inoculum had been added, there was a significant drop in retention to 22·5(2·2) per cent ($P < 0{\cdot}01$). At the third stage there was no further loss, but by the fourth stage there had been another significant decrease to 12·4(2·9) per cent ($P < 0{\cdot}05$) (*Figure 6*).

Perfusion-induced cell losses

Implantation in the superficial femoral artery led to a loss of seeded cells, from a mean(s.e.m.) of 12·7(3·4) to 7·0(1·5) per cent of harvested cells after 30 min (P not significant). By 24 h cell retention was essentially unchanged at 7·1(2·1) per cent. However, after 48 h it was 4·4(1·9) per cent ($P < 0{\cdot}05$) (*Figure 7*). Blood radioactivity did not rise above background levels.

Discussion

Mesothelial cell seeding did not reduce ^{111}In-labelled platelet deposition on Dacron 5 days after operation. This was expected because the technique had not produced confluent luminal cell cover until 4 weeks after similar grafts had been implanted in the canine aorta[7]. A similar finding has been reported for knitted Dacron preclotted with blood and endothelial cells, when at least 2 weeks are necessary for the cells to migrate through preclot to the luminal surface[18]. At 2 months mesothelial cell seeding failed to improve any of the measurements that confluent mesothelial cell cover should have produced. In this model the increased 6-keto-PGF$_{1\alpha}$ release[8] from seeded knitted Dacron explanted from the canine aorta at 6 weeks could not be confirmed. Both scanning electron microscopy and immunohistochemistry suggested that, irrespective of seeding, the flattened cells covering the grafts at 2 months were derived either from arterial endothelium or transmural ingrowth of capillaries. The mid-graft mesothelial cell cover observed in earlier studies of seeding did not develop[7].

The cell kinetics of seeding in this model were, therefore, investigated. ^{111}Indium oxine labels cells irreversibly by diffusing across the plasma membrane and binding cytoplasmic proteins[15,16]. The labelling efficiency was greater than for endothelial cells (25–75 per cent) but, since collagenase releases both mesothelial cells and blood cells from omentum, it is conceivable that it may have been improved by leucocyte and erythrocyte uptake[17,19]. The efficiency of mesothelial cell seeding was lower than that reported for endothelial cells at 14–62 per cent on similar grafts[17,19,20]. The factors that determine mesothelial cell seeding efficiency have not been studied but are likely to be the same as for endothelial cells, in which attachment to the graft surface is influenced by cell shape, basement membrane synthesis, graft surface conformation, ionic charge and the seeding technique employed[4,5].

Seeding Dacron by including mesothelial cells in the preclot was not an efficient method and the sequential seeding led to a net loss after the second aliquot of cells had been flushed through the graft. This has resulted in a move away from sequential to single-stage seeding[18,21,22]. The problem with seeding at preclotting and immediate graft implantation is that seeded cells are initially retained within the graft interstices by preclot and do not attach to the graft fibres. They may, therefore, be lost as the clot is washed away or lysed after implantation[23]. Subsequently, as attention focused on nonporous grafts such as polytetrafluoroethylene, single-stage seeding was modified to include a brief period of cell culture. Including this step made the technique more complicated because laboratory facilities were required. In the end, the technique remained flawed because there were insufficient numbers of cells to create confluent luminal cell cover at the time of surgery[4,5].

Confluent endothelial cell cover can be provided if seeding cells are harvested at a preliminary procedure and numbers increased during prolonged culture. Grafts are seeded by exposing the luminal surface to this excess of cells ('sodding') and then implanted at a second elective operation[24]. This two-stage technique prevents early platelet deposition[25]. Cell attachment can also be improved by precoating grafts with fibronectin, a glycoprotein synthesized by endothelial cells[20]. Collagen, blood, plasma and fibrin glue have been similarly successful[26]. A potential problem with fibronectin is that it also increases platelet adhesion, although this effect is of short duration and can be suppressed by antiplatelet therapy[27]. Precoating may also reduce perfusion-induced cell loss[19,28,29].

Mesothelial cell seeding could be changed to a two-stage technique. Omentum could be obtained at laparoscopy, cells harvested as described and cultured to produce the excess required for high-density seeding. However, the place of fibronectin in promoting mesothelial cell attachment to prosthetic materials has yet to be evaluated. Other therapeutic manoeuvres that would be worth applying include the use of immunosuppression to reduce host cytotoxic activity against seeded cells and the inhibition of host protease activity to preserve fibronectin[30,31].

Why mesothelial cell seeding should fail in the superficial femoral artery yet be successful in the aorta is difficult to explain, as the preclotting and seeding techniques were identical. The aorta, rather than the superficial femoral artery, might have been expected to yield favourable results with its higher shear rates and greater perfusion-induced cell loss. Graft crimping, however, might account for the difference because it involves a variable thickness of luminal thrombus and neointima, which could be an obstacle to cell migration. However, this is unlikely to have been important in the superficial femoral artery when <5 per cent of seeded cells remained on the graft[32] at 48 h.

Mesothelial cell seeding of preclotted knitted Dacron implanted in the canine superficial femoral artery did not influence thrombogenicity, patency or luminal cell cover. However, cell kinetic studies demonstrated that conditions in this model precluded realistic seeding densities. The technique of mesothelial cell seeding must be re-evaluated once critical seeding densities, cell attachment and cell retention after implantation have been achieved.

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Peripheral arterial thrombolysis: intermediate-term results

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To determine the intermediate-term results of intra-arterial thrombolysis, 127 consecutive patients receiving 129 courses of treatment were reviewed at a median follow-up of 3 years. At initial review, 30 days after treatment, thrombolysis was successful in 63 cases (49 per cent). Of these patients, 16 were lost to follow-up: 15 died without further vascular symptoms and one moved from the area. Some 35 patients were alive and asymptomatic, of whom 33 had either angiographic or clinical evidence of continued arterial patency. Symptomatic reocclusion occurred in 12 cases; a further two patients remained asymptomatic and reocclusion was detected at follow-up. Two of the 12 symptomatic patients required amputation. Estimated patency rates were 80 per cent at 1 year, 72 per cent at 2 years and 70 per cent at 3 years. The intermediate-term results in the 66 cases in which lysis was unsuccessful were worse, only 16 patients (24 per cent) surviving to follow-up with the treated limb intact. It is concluded that, if thrombolysis is successful at 30 days, the intermediate-term results are good.

In the treatment of patients with lower-limb ischaemia of recent onset, peripheral arterial thrombolysis has been shown to produce acceptable short-term results[1–4]. A few reports[5–7] have described results beyond 30 days. This study reviewed a consecutive series of 127 patients treated by intra-arterial thrombolysis, at a median of 3 years after treatment, to determine intermediate-term limb salvage rates after successful or failed thrombolysis, and the intermediate-term patency rate for successful lysis.

Patients and methods

Between March 1985 and August 1989, 127 consecutive patients had a total of 129 episodes of intra-arterial thrombolysis. All patients had suffered a sudden recent onset or deterioration of symptoms of lower-limb ischaemia within the preceding 60 days and all had ischaemic rest pain at presentation. In 55 of 129 cases no arterial blood flow could be detected at the ankle by Doppler ultrasonography and in a further 21 instances the pressure at the ankle was <50 mmHg; therefore, in 76 of the 129 episodes the patient suffered critical ischaemia at presentation. Clinical and arteriographic features of the patients before treatment are shown in *Table 1*. The technique used for lysis was as previously reported[8]; streptokinase was employed in 72 cases and recombinant tissue-type plasminogen activator (rtPA) in 57. Patients were assessed initially at 30 days and thrombolysis described as successful if the criteria shown in *Table 2* were met. Patients in whom thrombolysis had been successful received anticoagulation with warfarin for at least 6 months, with the exception of a few who had short lesions or a contraindication to anticoagulation who received low-dose aspirin.

All living patients were recalled for review between October 1990 and February 1991 at a minimum of 18 months after thrombolysis. They were assessed clinically and Doppler ultrasonography ankle: brachial pressure indices (ABPIs) recorded. Patients in whom lysis was successful at 30 days and in whom no subsequent reocclusion was demonstrated on angiography were invited to undergo localized digital subtraction angiography (DSA) to assess the patency of the recanalized segment. For patients who had died in the intervening period, the hospital records and, where necessary, general practitioner notes were reviewed. The date and cause of death, and the development of further vascular symptoms in the treated leg were noted.

For the purpose of analysis, when thrombolysis was repeated (two patients) each episode was treated independently. Limb salvage rates were calculated using life-table analysis[9]. Estimated patency rates are based on angiographic findings in 38 patients and clinical findings in the remaining 25, with a correction to allow for the possibility of asymptomatic reocclusion.

Results

The results at 30 days are shown in *Table 3*. At this initial assessment, lysis was successful in 63 cases, of whom 30 had undergone angioplasty of an underlying stenosis revealed by

Table 1 *Patient details*

Total no. of episodes of thrombolysis	129
Age (years)*	69 (25–96)
Sex ratio (M:F)	94:33
Patients with diabetes (%)	13
Duration of history (days)*	14 (1–49)
Ankle:brachial pressure index*	0·23 (0·00–0·80)
Length of occlusion (cm)*	16 (1–60)
Proximal limit of occlusion	
Common iliac artery	17
External iliac artery	7
Common femoral artery	14
Superficial femoral artery	63
Popliteal artery	23
Tibial arteries	2
Graft	3
Cause of occlusion	
Thrombosis	104
Embolus	17
Graft thrombosis	3
Postprocedural thrombosis	5

*Values are median (range)

Table 2 *Criteria for successful lysis*

Radiological evidence of lysis with arterial recanalization at least as far as the next major collateral
An increase in ankle:brachial pressure index $\geqslant 0{\cdot}2$
Limb salvage at 30 days without recourse to reconstructive surgery at the level at which lysis was performed
No clinical evidence of rethrombosis within the first 30 days (i.e. preservation of the increase in ankle:brachial pressure index)

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the thrombolytic therapy. Lysis failed in the remaining 66 cases. At follow-up, in 74 cases the patient was alive and available for review; 16 patients had undergone amputation of the treated limb. Of the remaining 55 cases, in 53 the patient had died before follow-up and in two the patients had moved from the area and were therefore lost to follow-up. The causes of death are shown in *Table 4*.

Intermediate-term results after successful lysis

The outcome at follow-up in the 63 cases in which lysis was initially successful is shown in *Figure 1*. One patient had moved from the area and was therefore not available for follow-up. Thirty-five patients survived to follow-up without developing further vascular symptoms; of these, 28 underwent intravenous DSA and patency of the treated segment was confirmed in 26 while asymptomatic reocclusion was demonstrated in two. Three patients declined review angiography and four did not attend; in all seven cases the increase in ABPI recorded after treatment was preserved at follow-up, suggesting continued patency. A further 15 patients died without reporting new vascular symptoms.

Further symptoms were reported in 12 cases at a median of 5·5 months after thrombolysis. Arteriography confirmed reocclusion in ten and the remaining two declined further investigation but had clinical evidence of reocclusion. Six of these patients were managed conservatively, and at follow-up one was asymptomatic, three suffered claudication and one had rest pain; the other patient died 36 months after thrombolysis, suffering from claudication at death. The remaining six patients had further intervention. One patient with a recurrent embolus 6 months after lysis underwent successful embolectomy and remained asymptomatic at follow-up. One patient in whom reocclusion occurred at 3 months underwent revascularization by further thrombolysis and was asymptomatic at death 32 months later. Three patients had femoropopliteal grafts after reocclusion: one graft remains patent and the patient asymptomatic, one patient developed claudication following graft reocclusion that persisted until death, and one patient required amputation after graft failure. The remaining patient underwent primary amputation. Therefore, although reocclusion occurred in a total of 14 of the 63 cases, only two patients subsequently required amputation.

Comparison between the 14 cases in which reocclusion was proven and the remaining 49 did not reveal any significant difference between the two groups. Both were of similar age at initial presentation: median 65·5 years for those with reocclusion *versus* 66·0 years for those with no reocclusion ($P = 0{\cdot}46$, Mann–Whitney U test). Both groups had similar duration of history, median 10·5 *versus* 14 days ($P = 0{\cdot}75$, Mann–Whitney U test). The ABPIs at presentation were similar, median 0·26 *versus* 0·29 ($P = 0{\cdot}27$, Mann–Whitney U test) as were the lengths of the occluded arterial segments measured by angiography, median 12 *versus* 14 cm ($P = 0{\cdot}73$, Mann–Whitney U test). A similar proportion of each group had received streptokinase as opposed to rtPA, seven of 14 in whom reocclusion occurred *versus* 22 of 49 in whom it did not ($\chi^2 = 0{\cdot}11$, 1 d.f., $P = 0{\cdot}72$). There were no significant differences between proportions of patients who had supra-inguinal sites of occlusion, four of 14 *versus* 16 of 49 ($\chi^2 = 0{\cdot}08$, 1 d.f., $P = 0{\cdot}78$) or who underwent angioplasty at the end of lysis, eight of 14 *versus* 22 of 49 ($\chi^2 = 0{\cdot}66$, 1 d.f., $P = 0{\cdot}43$).

The number of initial occlusions in this series that were embolic was small, 16 in total, of which seven were successfully treated. Reocclusion occurred in two: in one as a result of a recurrent embolus to the same leg and in the other due to *in situ* thrombosis.

Intermediate-term results after failed lysis

Of the 66 cases in which lysis was unsuccessful, 15 patients died within 30 days. Of these, two had amputation, four would have required amputation had they survived, and nine had viable limbs. A further 16 patients who were alive at 30 days had undergone major amputation, leaving 35 cases in which the patient was alive with the treated limb intact; in nine of these 35 cases reconstructive surgery had been carried out.

Table 3 *Results of 129 episodes of lysis at 30 days*

Outcome	No.
Overall limb salvage	
After successful lysis	63 (49)
After subsequent surgery	9 (7)
Despite failed lysis	26 (20)
Total	98 (76)
Major amputation	16 (12)
Death	15 (12)

Values in parentheses are percentages

Table 4 *Cause of death in 53 patients*

Myocardial infarction or other cardiac cause	11
Peripheral vascular disease	9
Bronchopneumonia	7
Stroke	3
Pulmonary embolus	3
Carcinoma of bronchus	3
Mesenteric infarction	3
Other	9
Unknown	5

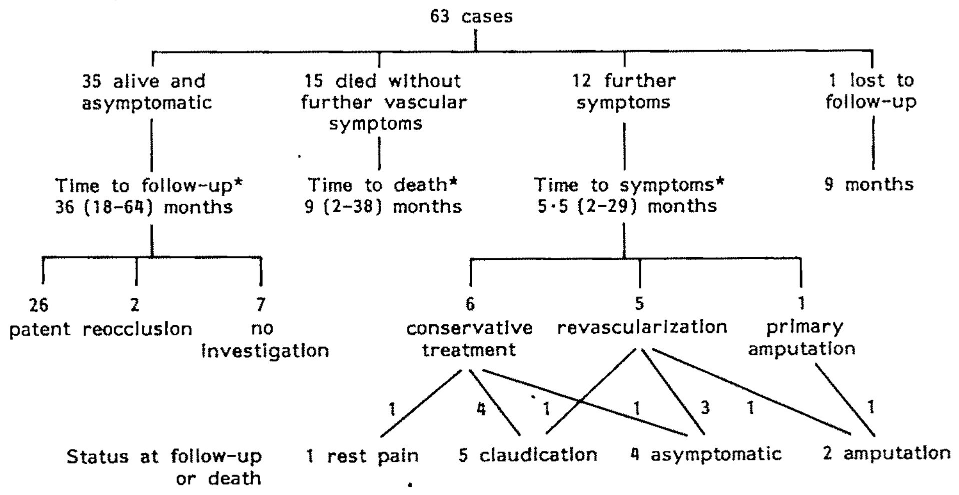

Figure 1 *Outcome at follow-up in 63 cases in which lysis was successful at 30 days. * Values are median (range)*

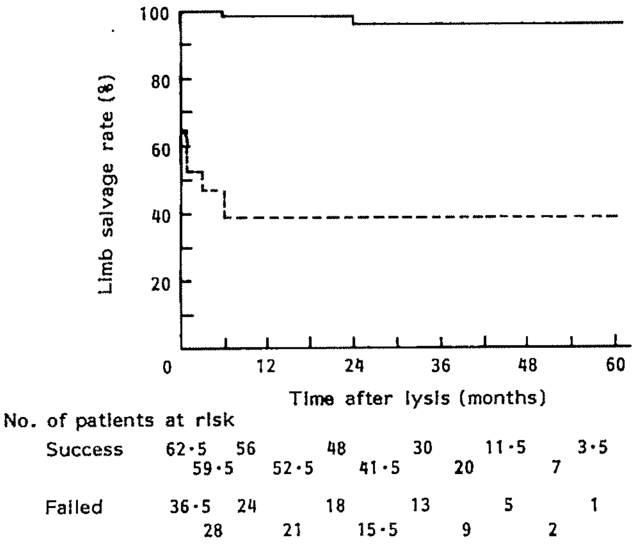

Figure 2 *Cumulative limb salvage rate for 63 cases of successful thrombolysis (——) and 66 of failed lysis (——). Patients who died with a limb that was judged to be non-viable are included as amputations*

During the follow-up period major amputation was performed in eight of these 35 cases at a median of 3 (range 0–8) months after thrombolysis; in four of these eight cases the patient survived to follow-up. A further ten patients died between initial review and follow-up: four as a direct result of lower-limb ischaemia and six from other causes, with the treated limb intact and viable. One patient was lost to follow-up. Therefore, only 16 patients in whom lysis failed remained alive with the treated limb intact and viable at follow-up at a median of 38 (range 19–64) months after thrombolysis (*Figure 2*). Eight of these patients were asymptomatic, six suffered claudication and two had rest pain.

Late complications

Late complications, possibly attributable to treatment with thrombolysis, were seen in two patients. One presented with a false aneurysm at the femoral artery puncture site 1 month after thrombolysis. The other patient developed a large retroperitoneal haematoma 10 months after lysis while receiving warfarin. This resulted in femoral nerve compression and damage, with subsequent permanent quadriceps wasting. At surgical exploration, this haematoma appeared to have arisen spontaneously; it was noted that it did not appear to originate from the previous femoral artery puncture site.

Discussion

If intra-arterial thrombolysis is to gain more widespread acceptance for the treatment of recent arterial occlusion it must be shown to be comparable to, or better than, the alternative surgical treatment in the short, intermediate and long term. There are few data available on the long-term results of surgical treatment in patients with recent arterial occlusion comparable to the present group. Long-term results are available for the surgical treatment of chronic lower-limb ischaemia and the best data suggest that 3-year patency rates of up to 80 per cent are achievable[10–12]. However, it is likely that patency rates in patients with acute or acute on chronic lower-limb ischaemia are much lower than this.

Percutaneous recanalization of chronic long-segment arterial occlusion by transluminal angioplasty alone or in conjunction with laser treatment is associated with a disappointingly high rate of restenosis[13,14]. This has been attributed largely to platelet deposition at the site of angioplasty with subsequent release of mitogens including platelet-derived growth factor. Patients in the present series had long-segment thrombotic occlusions (median length 12 cm in those undergoing successful recanalization). The potentially deleterious effect of mitogens released from these platelet-rich occlusions has led to fears that successful recanalization by thrombolysis may be complicated by a high incidence of late restenosis. This has not proven to be the case. The primary patency rates in the present study, after successful recanalization at 1 month, were approximately 80 per cent at 1 year, 72 per cent at 2 years and 70 per cent at 3 years, with an excellent rate of limb salvage (*Figures 2* and *3*). These patency rates are similar to those reported by Hess *et al.*[5,6]. In that study[6] intermediate-term patency was assessed in 313 limbs in which lysis had initially been successful at 2 weeks, by ultrasonography or questionnaire with Doppler ultrasonography in those reporting deterioration. Reported overall patency rates were 80 per cent at 1 year, 74 per cent at 2 years, 70 per cent at 3 years and 63 per cent at 5 years. Better patency rates have been reported by Lammer *et al.*[7]: 86 and 81 per cent at 1 and 2 years respectively. This apparent superiority may be due to patient selection for thrombolysis, because patients without demonstrable run-off were excluded.

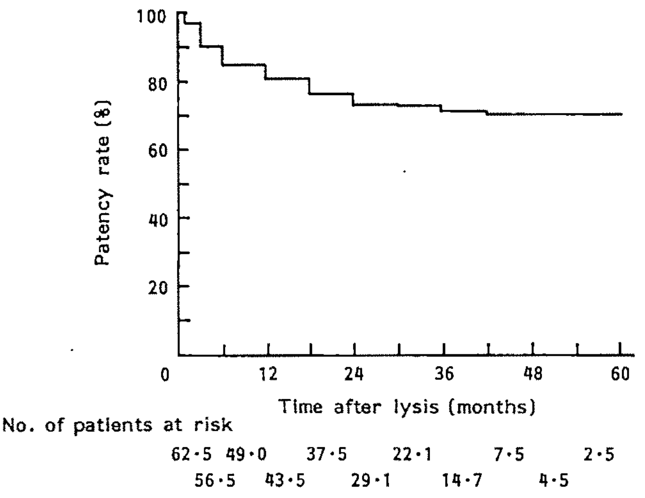

Figure 3 *Estimated cumulative primary patency rate of the treated arterial segment in 63 cases in which lysis was successful. Patency data could not be obtained in 23 asymptomatic patients because of death (15 patients), or refusal or unavailability to undergo review arteriography (eight, including one lost to follow-up). The cumulative patency rate was estimated by assuming that the reocclusion rate in these 23 patients was the same as in the 28 asymptomatic patients in whom patency data were available, i.e. approximately one occlusion every 500 months of patency*

In comparison with the present good intermediate-term results after successful lysis, those after failed lysis are poor. This difference in outcome between patients who fulfil the strict criteria for successful lysis and those who do not supports the use of these criteria.

In conclusion, good intermediate-term results after peripheral thrombolysis are obtainable when treatment is initially successful. The present data, in conjunction with an increasing number of reports showing acceptable short-term results from the technique, support the more widespread use of intra-arterial thrombolysis.

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Announcement

Peter Clifford Travelling Scholarship

The 1992 Vascular Travelling Scholarship of £1000, presented in memory of Peter Clifford, consultant vascular surgeon at Frenchay Hospital, Bristol, has been awarded to Mr Nicholas Cheshire of St Mary's Hospital, London, to support a visit to Seattle, Washington, USA.

Mr Cheshire will give the second Peter Clifford Memorial Lecture during the President's Day meeting of the Royal Society of Medicine Section of Surgery on 28 May 1993 at St Mary's Hospital (Cockburn Theatre) at 3.30 p.m. The lecture is entitled 'Aspects of molecular biology and atherogenesis in Seattle'. All are welcome to this lecture and also to attend the rest of the day, courtesy of Mr David Rosin, President of the RSM Section of Surgery. This invitation extends to dinner in the evening.

For further details of this lecture, President's Day and the 1993 Peter Clifford Travelling Scholarship, please contact Mr Peter McDonald, Department of Surgery, Northwick Park Hospital, Harrow, Middlesex HA1 3UJ. Telephone: 081 869 2627.

P. McDonald

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Tissue and urokinase plasminogen activators in the environs of venous and ischaemic leg ulcers

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Urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) were assayed in biopsies from the base, edge and adjacent skin of ischaemic and venous ulcers using a functional bioimmunoassay and a standard immunoassay. Two series of 14 biopsies were examined: from seven venous and seven ischaemic ulcers in the first series, eight venous and six ischaemic in the second. It was found that tPA was detected in only four samples of ulcer edge using the bioimmunoassay and in no sample by the standard immunoassay. By contrast, uPA was detected in all but one ulcer edge biopsy and at a significantly lower median concentration in the adjacent skin (16·9 units/g) than the ulcer edge (26·1 units/g) or base (32·3 units/g) (both $P < 0{\cdot}01$)*. Levels of uPA were greater in the edge and base of venous compared with ischaemic ulcers. The predominant plasminogen activator in chronic leg ulcers is uPA; this activator may play an important role in wound healing.*

The cause of delayed healing of venous ulcers is uncertain and has excited little interest. One study reported that epidermal mitosis and cell migration occurred at similar rates in the edges of healing and 'non-healing' venous ulcers[1]. This observation led to the suggestion that delayed re-epithelialization was caused by an increased loss of epidermal cells from the ulcer surface, which might occur from a failure of keratinocytes to adhere to the underlying ulcer base.

Type IV collagen and laminin are basement membrane proteins present in normal skin that are thought to have a role in epithelial cell adherence[2,3]. Both these proteins have been shown to be deficient beneath migrating epidermal cells[4,5]. Animal studies have suggested that fibrinogen and fibronectin are the predominant proteins in the basement membrane zone at the edge of re-epithelializing cutaneous wounds[6,7]. Fibrinogen and fibronectin mediate the adherence of epithelial cells to culture plates[8,9] and are degraded by the action of plasmin[10,11], which also plays a role in the breakdown of intercellular linkages[12]. Plasmin degrades laminin[13] and activates collagenases, which degrade collagen[10]. Abnormal levels of plasmin, plasminogen and plasminogen activators might therefore be found in the environment surrounding cutaneous ulcers and may account for poor cellular adherence to the ulcer base in poorly healing venous ulcers. Plasmin is derived in blood and tissues from its precursor, plasminogen, by the action of the two plasminogen activators: tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). The biological activity of these may be abolished by plasminogen-activator inhibitors[14], which have different affinities for tPA and uPA.

In patients with venous ulceration there is an altered level of systemic and vein wall fibrinolytic activity. There are no data on tissue levels of plasminogen activators in chronic cutaneous ulcers[15]. Vein wall releases tPA, which is the predominant plasminogen activator in blood[16]. This may have little influence in the chronic ulcer, however, because uPA is more responsible for remodelling tissues[17].

This study examined the presence, biologically active (functional) levels, and type of plasminogen activators in the base and edges of cutaneous ulcers and in the adjacent intact skin. Venous and ischaemic ulcers were studied to discover whether variation in the quantities of plasminogen activator occurred with different pathological processes.

Patients and methods

Patients with cutaneous leg ulcers that had not reduced in surface area during at least 12 weeks of conservative outpatient treatment were admitted for surgery. Those with venous ulcers had these excised and grafted; patients with ischaemic ulcers underwent vascular reconstruction or amputation. At surgery, a biopsy was taken from the edge of the ulcer. Wet saline-soaked dressings were used before surgery and no patient was taking medication known to alter systemic fibrinolytic activity. The cause of each ulcer was determined from clinical history, examination and investigations including full blood profile, erythrocyte sedimentation rate, urea and electrolyte levels, liver function tests, rheumatoid factor latex fixation test, Rose–Waaler titre, antinuclear antibody titre and ankle:brachial Doppler arterial pressure index (ABPI). The diagnosis of venous ulceration was accepted in the absence of another cause when there were post-thrombotic changes on ascending phlebography or when an abnormal half-volume refilling time was recorded on foot volume plethysmography[18].

Biopsies

Biopsies approximately 3 mm thick were taken from the edge of each excised ulcer. Two series of assays were performed. In the first, two biopsies were taken: a 2-mm wide piece of the ulcer base and a 2-mm width of adjacent intact skin. In the second series of assays, 2-mm wide biopsies were taken from the ulcer base adjacent to the re-epithelializing edge, a width including the ulcer edge, and a 4-mm width of intact epithelium adjacent to the ulcer edge. Biopsies were frozen in liquid nitrogen and stored at −70°C to prevent loss of activator activity. At a later stage, 0·05 g of each segment was homogenized using a Mikrodismembrator II (Braun, Melsungen, Germany) and mixed with 2 ml phosphate-buffered saline at pH 7·4. These samples were stored at −70°C until batches of assays were performed. The samples were thawed, centrifuged at 3000 r.p.m. for 5 min and 100 μl of the supernatant used for each assay.

Immunoassays

Determination of tPA and uPA was by two bioimmunoassays[19] that measured the biologically active levels of each activator. To obtain an indication of the presence of plasminogen-activator inhibitors an immunoassay for tPA was performed[20]. The difference between functional and immunological levels of tPA was taken as an indicator of the presence of inhibitor. International standards for tPA and uPA were used to calibrate these assays. During this study plasminogen-activator inhibitor assays did not allow an accurate measure of inhibitor.

The functional immunoassay was dependent on the tPA or uPA in each sample being bound to the immobilized immunoglobulin (Ig) G fraction of polyclonal sera against tPA or uPA that was coated on

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multiwell plates. Plasminogen was added to the plates and the plasmin generated by the action of plasminogen activator not bound by inhibitors was detected by its effect on a chromogenic substrate (S2251; Kabi Pharmacia, Stockholm, Sweden). The results were read as an optical density and calibrated against dilution curves using the World Health Organization standards of tPA and uPA.

The second immunoassay differed from the first by the addition of a second antibody to the plasminogen activator, conjugated to alkaline phosphatase instead of plasminogen. This bound to all the plasminogen activator present and the alkaline phosphatase acted on an added chromogenic substrate. The results were again read as an optical density.

The results of both assays are expressed as units per gram tissue.

Study design

Twenty-eight ulcers were assessed, 14 by each biopsy technique. In the first series there were seven venous and seven ischaemic ulcers. In the second series there were eight venous and six ischaemic ulcers. Three of the patients with venous ulcers in the first series had a subsequent ulcer episode and biopsy, and were included in the second series. All investigations were repeated before the second biopsy. The median ABPI of limbs with ischaemic ulcers was 0·48 (range 0·21–0·74). The median half-volume refilling time of limbs with venous ulcers was 4·2 (range 0·0–10·5) s.

Separate biopsies incorporating the ulcer base and edge as well as intact skin were taken from five ulcers (three venous, two ischaemic) and examined by immunofluorescence using a rabbit polyclonal antibody to uPA that was used to coat the multiwell plates (dilution 1:10; from Dr P. J. Gaffney, National Institute for Biological Standards and Control). This was a two-stage procedure using fluorescein isothiocyanate-labelled antirabbit IgG (dilution 1:200; Dako, High Wycombe, UK) in the second stage. The sections were examined to determine the major site of uPA and to compare the fluorescence for uPA in the basement membrane zone at the ulcer edge with that of intact skin. The level of fluorescence in the epithelium at the ulcer edge was compared with that in intact skin on the same biopsy.

The study protocol was approved by St Thomas' Hospital Ethics Committee. Statistical analysis was by non-parametric methods using the Wilcoxon rank sum test for unpaired data and Wilcoxon signed rank test for paired data.

Results

First series of biopsies

Detectable levels of tPA were present in only one biopsy from the ulcer edge (ischaemic ulcer) and in only five from adjacent skin samples (four ischaemic, one venous) using the bioimmunoassay, the lower limit of the assay being 3·1 units/g. Levels of tPA measured by the standard immunoassay were below the lower limit of detection (16 units/g) in all samples.

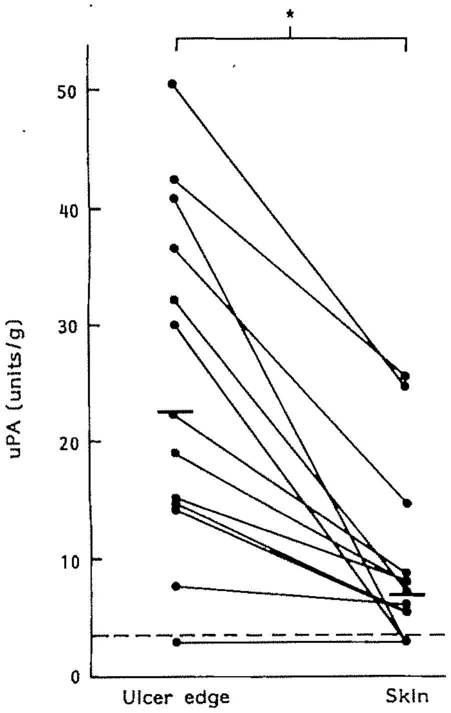

Figure 1 *Urokinase plasminogen activator (uPA) levels in samples from ulcer edge and intact skin in the first series of biopsies. Bars are medians; ---, limit of sensitivity of assay.* *P < 0·01 *(Wilcoxon signed rank test)*

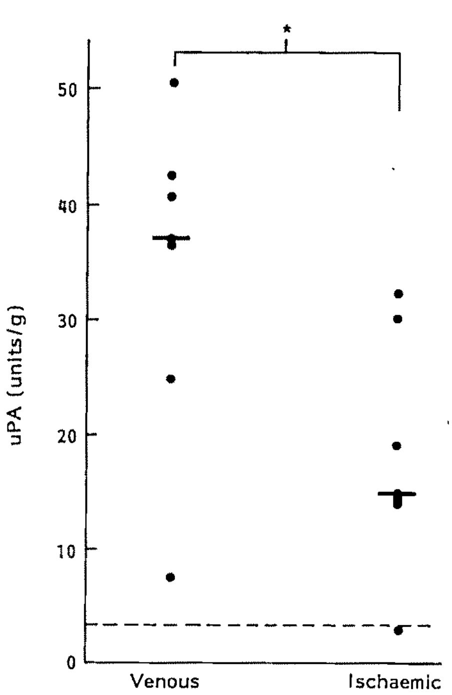

Figure 2 *Urokinase plasminogen activator (uPA) levels in samples from the edge of venous compared with ischaemic ulcers in the first series of biopsies. Bars are medians; ---, limit of sensitivity of assay.* *P < 0·05 *(Wilcoxon rank sum test)*

The bioimmunoassay detected uPA in all but one sample from the ulcer edge (ischaemic ulcer) and in all but three samples from the adjacent skin (two ischaemic, one venous). In one ulcer (venous) the intact skin sample was inadequate for plasminogen-activator assay. The median (range) uPA level in samples from the ulcer edge was 22·2 (<3·1–50·5) units/g; in samples from adjacent skin this value was 7·1 (<3·1–25·3) units/g. The concentrations detected in the ulcer edge were significantly greater ($P < 0{\cdot}01$) than those in the surrounding tissues (*Figure 1*). The median (range) quantities of uPA measured in biopsies taken from the edge of venous ulcers were significantly greater than those found in ischaemic lesions (37·0 (7·7–50·5) *versus* 15·0 (<3·1–32·3) units/g, $P < 0{\cdot}05$) (*Figure 2*). A similar difference was not seen in the surrounding skin.

Second series of biopsies

Levels above the lower limit for the tPA bioimmunoassay (3·1 units/g) were found in only three samples taken from the ulcer edge (venous), in three samples from intact skin (venous) and in none of those from the ulcer base. No tPA was detected by the standard immunoassay.

In this series of biopsies, uPA was detected by bioimmunoassay in all but one of the samples from the ulcer base (ischaemic), in all samples from the ulcer edge and in all but one of those from adjacent skin (venous). There was no significant difference in median (range) uPA concentration in samples from the ulcer base compared with those from the ulcer edge (32·3 (<3·1–92·6) *versus* 26·1 (11·8–200·0) units/g, $P > 0{\cdot}10$). Levels of uPA were, however, significantly lower in samples taken from adjacent skin (median 16·9 (range <3·1–47·9) units/g) than in those obtained from the other two sites (both $P < 0{\cdot}01$; *Figure 3*).

The uPA levels in samples from the base and edge of venous ulcers were significantly higher than in similar samples from ischaemic lesions (*Table 1*). Levels in the surrounding tissues of both types of ulcer were similar.

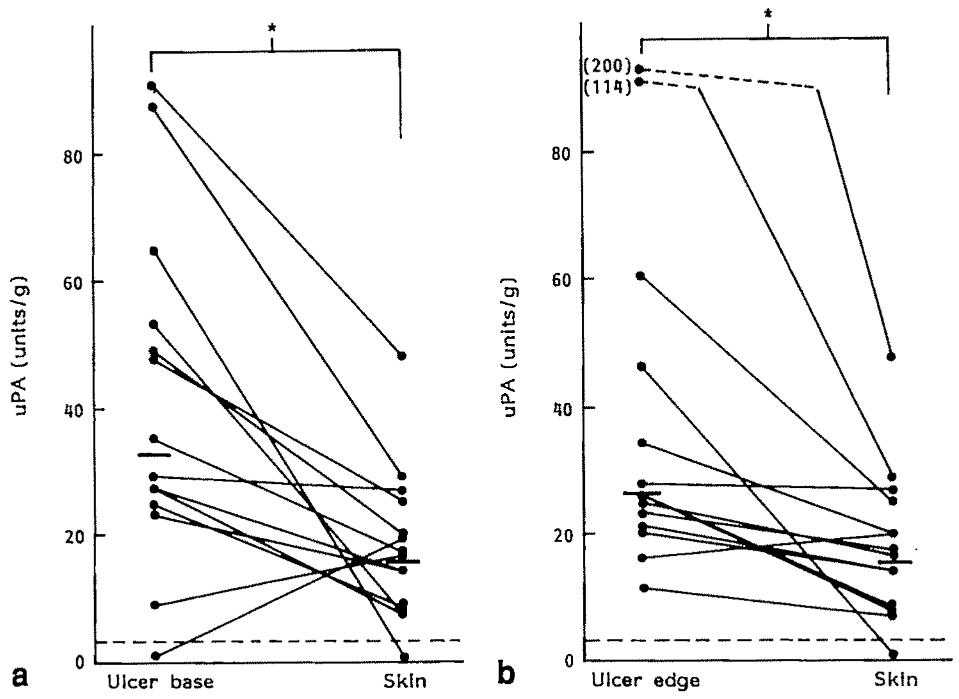

Figure 3 *Urokinase plasminogen activator (uPA) levels in* **a** *ulcer base and adjacent skin samples and* **b** *ulcer edge and adjacent skin samples in the second series of biopsies. Bars are medians; ----, limit of sensitivity of assay.* *P < *0·01 (Wilcoxon signed rank test)*

Table 1 *Urokinase plasminogen activator levels in samples from the base and edge of venous and ischaemic ulcers*

	Base (units/g)	Edge (units/g)
Venous ulcers	51·2 (8·9–92·6)	40·6 (21·4–200·0)
Ischaemic ulcers	26·1 (<3·1–35·3)	22·0 (11·1–27·9)

Values are median (range)

Biopsies examined by immunofluorescence using antibodies to uPA demonstrated minimal staining in the basement membrane zone in the ulcer edge compared with intact skin. There was staining in the epidermis in the advancing epithelium that was absent in intact skin; the bulk of the staining occurred in the granulation tissue.

Discussion

This study demonstrates significantly raised levels of functionally and immunologically active uPA in the base and edges of venous and ischaemic ulcers compared with adjacent intact skin. As undetectable or very low levels of tPA were found in the edges and base of only a few ulcers it would seem that uPA is selectively localized in and around cutaneous ulcers. The failure to detect tPA by immunological assay indicates that there is little or no plasminogen-activator inhibitor present in and around cutaneous ulcers. These results suggest that the standard immunological assay is less sensitive than the bioimmunoassay. The studies should be repeated using a specific plasminogen-activator inhibitor assay.

In both sets of assays there were higher concentrations of uPA in the edge and base of venous compared with ischaemic ulcers. Ischaemia may reduce the ability of the granulation tissue or keratinocytes to produce urokinase, which may be of importance in ulcer healing.

The two plasminogen activators are the product of different genes on different chromosomes[21,22] and appear to have different actions. It is known that tPA is produced by endothelial cells[16] and is responsible mainly for thrombolysis, whereas uPA appears to influence cell migration, tissue degradation, remodelling and invasion by acting as a key enzyme in breakdown of the extracellular matrix[17]. It has been assumed that in venous disease the impaired systemic fibrinolytic activity results from an alteration in tPA release from venous endothelial cells. The present study, however, shows that in tissue uPA appears to be the predominant plasminogen activator. Further work is required to assess the uPA levels at the edges and base of healing cutaneous ulcers in otherwise healthy legs before definite conclusions can be drawn.

The role of high concentrations of uPA in the base and edges of cutaneous ulcers is open to speculation. Increased amounts of plasminogen activators may influence the adherence of epithelial cells through the action of plasmin, which can degrade intercellular linkages. They may also digest proteins in the basement membrane zone that are thought to mediate epithelial cellular adherence[10–13]. Keratinocytes produce plasminogen activators and contain almost exclusively uPA in the epithelial outgrowths that occur after wounding[17]. It has been suggested that keratinocytes may use plasmin activated by uPA to 'dissect' a way through the fibrin and fibronectin matrix during healing. High levels of plasminogen activators may contribute to the process of wound contraction by preventing rigid attachment of epithelial cells to the basement membrane zone. If the quantities of local plasminogen activators are abnormal, however, they may impair epithelial cell adherence and cause excessive cellular loss and delayed wound healing. The presence of uPA may simply reflect the amount of fibrin deposited in the tissues as part of the healing process, where it may be required to act as part of the homoeostatic mechanism by breaking down the deposited fibrin during healing[23]. It may, alternatively, be a marker for the degeneration of epithelial cells, as has been suggested to explain similar findings in the epithelial cells of gastric mucosa[24]. It may be that uPA is acting as a growth factor[25] to stimulate epithelial cellular division. This action may be related to the homology between plasminogen activators and epidermal growth factor[26] and has been suggested as one of the main reasons why urokinase is associated with malignancy.

Preliminary work using immunofluorescent techniques to identify uPA in cutaneous ulcers has suggested that this activator is present predominantly in granulation tissue, where it is diffusely distributed. This technique has also indicated that there is a relative paucity of uPA in the basement membrane zone at the edge of an ulcer compared with intact skin. These results endorse the finding that epithelial cells are producing uPA[17].

The present study does not indicate whether the high levels of plasminogen activator are abnormal and related to defective healing or whether they are part of the normal healing process. It does indicate that attempts to enhance systemic fibrinolytic activity to improve ulcer healing[27,28] are unlikely to influence the tissue fibrinolytic activity, which is already high. This is supported by a previous study, which has shown that there is little relationship between tissue and systemic fibrinolysis[29].

If plasminogen activators are important in cutaneous ulcer healing, manipulating local levels of uPA could influence the rate of healing. Agents such as stanozolol and defibrotide have been used to manipulate systemic fibrinolytic activity but their effect on tissue fibrinolysis has not been demonstrated.

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Long-term circulatory access via a peripheral implantable port

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The use of a novel indwelling central venous catheter system is described which combines the safety of peripheral venous catheter placement with a novel electromagnetic locator device for guidance of the catheter tip into the correct position. This locator system obviates the need for radiological screening or chest radiography for checking catheter placement. Fifty-one patients were studied prospectively and all were successfully cannulated. An infection rate of 0·29 per 1000 catheter-days was seen with a mean system life of 220 (range 15–510) days. The new port has a lower infection rate than other commonly used systems and eliminates complications such as pneumothorax and puncture of major arteries.

Long-term venous access can be maintained using an indwelling catheter in a central vein[1]. In the 1980s, totally implantable chest-wall vascular access ports were introduced. However, central venous cannulation was still required for insertion of indwelling catheters and chest-wall implantable systems, complications such as arterial puncture and pneumothorax were frequently encountered[2], and radiological screening was required during catheter insertion to ensure correct positioning.

Recently, a system for long-term vascular access via a peripheral implantable port was introduced that combines the advantages of implantable access devices with the safety of peripheral venous cannulation. Initial experience with this new technique is presented.

Patients and methods

Patients

Between August 1990 and December 1991, 51 consecutive patients requiring long-term circulatory access were entered into the study; there were 38 men and 13 women of mean age 51 (range 27–81) years. The diagnosis was malignant disease in 37 patients and acquired immune deficiency syndrome in 14. The diagnosis and indications for circulatory access are shown in *Table 1*.

Materials

The peripheral implantable system (PAS Port; Pharmacia Deltec, Milton Keynes, UK) consists of a titanium port with a self-sealing septum and polyurethane catheter. The catheter is 76 cm long with an external diameter of 1·9 mm and an internal diameter of 1·05 mm. It contains a sensor wire, the tip of which is capable of detecting an electromagnetic field. Catheter placement is verified by an electronic locating system (Cathfinder; Pharmacia Deltec). This consists of a hand-held locator or 'wand' connected to a central console. When activated, the wand emits an electromagnetic field. It is passed over the body surface, along the course of the catheter. The catheter sensor tip detects the signal and transmits the information back to the control system via the sensor wire. When the wand reaches the external location of the sensor tip an audible beep is emitted and an indicator light on the wand changes colour.

Table 1 *Patient diagnosis and indications for circulatory access*

Diagnosis	No. of patients	Indication
Metastatic colorectal cancer	24	Chemotherapy
Acquired immune deficiency syndrome	14	Antiviral therapy
Malignant melanoma	5	Chemotherapy
Oesophageal cancer	5	TPN, chemotherapy
Gastric cancer	3	Chemotherapy

TPN, total parenteral nutrition

Insertion

Under aseptic conditions and local anaesthesia the basilic vein of the non-dominant arm is dissected and placed in slings. The vein is cannulated with the catheter–sensor wire assembly and the catheter advanced to the level of the superior vena cava (approximately 50–55 cm). The position of the catheter tip is confirmed by passing the hand-held locator device over the body surface, along the arm and over the chest. The catheter can be repositioned if necessary, using the same procedure, until a satisfactory location is obtained. The sensor wire is then withdrawn from the catheter. A subcutaneous pocket is fashioned in the forearm and the catheter connected to the outlet tube of the titanium port which is then flushed with 10 ml heparinized saline (200 units/ml). The port is sutured to the base of the subcutaneous pocket and the skin incision closed using interrupted monofilament sutures.

Port access and catheter care

Using a strict aseptic technique a sterile non-coring needle is advanced through the septum; a characteristic sensation is noted as the needle traverses the chamber and comes into contact with the metal floor. Straight or 90° 20- and 22-G needles are available; the 90° needle can be taped to the patient's forearm for prolonged infusion. The silicone septum is designed to withstand approximately 800 punctures without sustaining structural damage. The system is flushed with 5 ml heparinized saline (200 units/ml) before and after each infusion. When not in regular use, monthly heparin flushes are required to maintain patency.

Results

Fifty-one patients were entered into the study and all were eventually successfully cannulated (intention to treat rate 100 per cent). Two attempts were required in two patients and three in a third. Failure to cannulate resulted from difficulty in advancing the catheter beyond the clavipectoral fascia in two patients and gross venous thrombosis in an intravenous drug abuser, although the procedure succeeded in an alternative vein on the same arm or the other arm.

All systems functioned after implantation and there were no complications associated with insertion. The final position of the catheter tip, determined by the electronic locator device, was satisfactory in all patients. Postoperative chest radiography confirmed there was no malposition of the catheter tip in the first 20 patients. Chest radiography was not performed in the other 31 patients.

The mean lifetime of the system to date is 220 (range 15–510) days and the longest follow-up 17 months with a cumulative

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experience of 6886 catheter-days. None of the systems has been electively removed. Twenty-five patients died with the system *in situ* while undergoing treatment. Four patients with advanced malignancy discontinued treatment because of progressive disease but wished to retain the port in the hope of receiving further treatment. Twenty-two continue to receive treatment.

Five complications have occurred in four patients, a complication rate of 0·73 per 1000 catheter-days. One patient developed an axillary vein thrombosis 8 days after insertion that was confirmed venographically. The system was removed and the thrombosis responded to anticoagulation treatment. One patient infected with human immunodeficiency virus developed non-infective thrombophlebitis 2 days after implantation which failed to settle with conservative management. The system was removed on day 14 and the phlebitis resolved a few days later. One incident of late thrombophlebitis that occurred 3 months after catheter insertion settled on conservative therapy. Two patients developed late staphylococcal port-pocket sepsis requiring exploration. The overall sepsis rate was therefore 0·29 per 1000 catheter-days, affecting 4 per cent of patients. To date, there have been no episodes of systemic sepsis, catheter occlusion or fluid extravasation.

Discussion

The technical developments of Broviac *et al.*[1] and Hickman and colleagues[3] permitted the widespread use of prolonged venous cannulation. Direct percutaneous subclavian insertion of these catheters is associated with damage to surrounding structures such as pneumothorax and subclavian artery injury, and malposition of the catheter occurs at a rate of 2 per cent[2]. Once *in situ*, the most common complications are exit site infection in 1–10 per cent, systemic line sepsis in 3–10 per cent, catheter occlusion in 0–8 per cent and major vessel thrombosis in 2 per cent[2,4–7]. From the patient's viewpoint, externally sited catheters can be distressing, socially restricting and may require frequent tedious maintenance procedures.

Totally implantable venous access systems have been well received by clinicians and patients, although direct central venous access is still required for catheter insertion and attendant complications may still occur. Furthermore, screening radiology is required for confirmation of catheter position and full operating theatre facilities may be needed. Once implanted, however, these systems are subject to fewer infective complications than their externally sited counterparts. Port-pocket infection rates of 0–15 per cent have been found with total infection rates[8] of 0–1·8 per 1000 catheter-days. Most investigators report catheter occlusion in 3–10 per cent of chest-wall implantable systems and major vein thrombosis in 0–5 per cent.

Experience with the peripheral implantable system shows several advantages over other techniques. The device is inserted under local anaesthesia in the antecubital fossa and, in the authors' experience, the implantation procedure has been complication-free. The rapid and reliable confirmation of catheter tip location using the electronic tracking system obviates the need for cumbersome, time-consuming and expensive radiological screening. The peripheral access system can be implanted outside the theatre setting.

Two previous reports[9,10] have described this technique with a success rate for antecubital vein cannulation of 84–94 per cent on an intention to treat basis compared with 100 per cent in the present study. The reported infection rate of 3–5 per cent is comparable to the 4 per cent in the present series and major vessel thrombosis was seen in 6 per cent of systems.

Nursing staff were able to utilize the system with ease in the hospital and community setting. Several patients have been able to access their own systems beyond the hospital environment and no episodes of fluid extravasation were seen. This peripheral access system combines the advantage of implantable ports with the safety and simplicity of peripheral cannulation. The initial outlay on the electromagnetic tracking device (>£1000) may be offset by the reduction in radiology costs. The performance of the ports exceeds that of externally sited catheters and matches that of chest-wall ports at an equivalent cost but avoids the complications attendant on direct central venous cannulation.

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Results of a prospective randomized trial of the Angelchik prosthesis and of a consecutive series of 119 patients

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The results of a randomized multicentre trial comparing the Angelchik prosthesis with floppy Nissen fundoplication for gastro-oesophageal reflux were assessed 4–6 years after surgery. Of the original 52 patients 48 were traced. A good or excellent result (Visick grade 1 or 2) was obtained in 21 of 25 after insertion of the Angelchik prosthesis compared with 18 of 23 after fundoplication. Poor results were due to recurrent heartburn after fundoplication and to dysphagia after prosthesis insertion. In a separate consecutive series of 119 patients receiving Angelchik prostheses, results were good or excellent in 101 (85 per cent) and poor in 18 (15 per cent). Control of reflux with a correctly positioned prosthesis was good. Troublesome dysphagia (Visick grade 3 or 4) was experienced in eight of the 119 patients. There was no mortality and no incidence of splenectomy or gas-bloat syndrome.

Angelchik and Cohen[1] first described a novel antireflux prosthesis in 1979, since when over 25 000 have been inserted. So far only three randomized controlled trials have compared the results with this prosthesis with those of Nissen fundoplication in adults[2–4]. The first trial[2] of 52 patients showed that 96 per cent of those receiving an Angelchik device achieved Visick grade 1 or 2 compared with 81 per cent of those undergoing fundoplication. The subsequent two trials[3,4] found better results using Nissen fundoplication and the results with the Angelchik prosthesis were worse than in the original study. Although none of these trials found a significant difference between the two antireflux procedures, the Angelchik prosthesis continues to receive adverse editorial comment[5,6]. The present paper provides further information on which to judge the place of this device. The results of the original multicentre trial[2] were reassessed after 4–6 years and the outcome in the next 119 consecutive patients determined.

Patients and methods

Prospective randomized trial

All patients had gastro-oesophageal reflux on barium meal examination and oesophagitis on endoscopy with persistent symptoms after medical treatment. Patients were randomized to undergo insertion of an Angelchik prosthesis (group 1) or Nissen fundoplication as modified by Donahue *et al.*[7] (group 2). Operative details have been given elsewhere[2].

Clinical and endoscopic assessments were performed by one clinician who had not met the patients previously and was unaware of the type of operation performed. Macroscopic oesophagitis was assessed using the classification of Savary and Miller[8]. A total of 52 patients were included in the original trial but four were lost to follow-up. The remaining patients were all traced. Three had died from unrelated disease but had been assessed clinically within 6 months of death. The remaining 45 patients were interviewed and all but three underwent endoscopy and biopsy.

Consecutive series

Since closure of the above trial further patients requiring antireflux surgery have received an Angelchik prosthesis. If perioesophageal fibrosis from previous surgery made dissection hazardous these patients underwent antrectomy and Roux-en-Y diversion[9]. The mean age of the 119 patients in whom an Angelchik prosthesis was inserted (group 3) was 54·4 (range 12–84) years. The mean length of follow-up was 3 years 3 months (range 5 months to 7 years 5 months). Patients underwent interview and endoscopy by the same observer, who had not performed any of the operations. Preoperative and follow-up symptoms were assessed and scored using a modified Visick grading[10]. A plain abdominal radiograph was obtained to check the position of the radio-opaque Angelchik prosthesis. All preoperative and postoperative oesophageal biopsies were reviewed independently and scored for evidence of reflux oesophagitis[11]. Eight patients were not interviewed but clinical data were obtained from the records of the last consultant outpatient assessment. Seventeen patients did not undergo endoscopy at follow-up and good-quality squamous epithelial biopsies from both preoperative and follow-up examinations were available for histopathological evaluation in only 84. Clinical details of patients in group 3 are summarized in *Table 1*.

Table 1 *Clinical details of 119 consecutive patients receiving an Angelchik prosthesis (group 3)*

	No.
Dysphagia	35
Severe regurgitation with nocturnal choking	22
Preoperative oesophageal dilatation	12
Sliding hiatus hernia	96
Rolling hiatus hernia	3
Barrett's oesophagus (>3 cm of columnar-lined oesophagus)	17
Widened hiatus at surgery (>3 fingers' breath)	54
Anterior plication of crura at surgery	48

Results

Prospective randomized trial

Clinical results are shown in *Table 2*. Twenty-one of the 25 patients achieved good or excellent results in group 1 compared with 18 of 23 in group 2. Dysphagia was the principal cause of all unsatisfactory results in group 1 and was the predominant symptom in all patients with Visick grades 3 and 4. Nine patients in group 1 had minimal dysphagia that could be avoided by chewing food well. One patient in group 1 complained of significant recurrent heartburn (Visick grade 3). Unsatisfactory results in group 2 were attributed mostly to recurrent heartburn and regurgitation, especially in patients scoring Visick grade 3 or 4. Gas bloat did not occur in group 1 patients but in three in group 2.

Complications. In three patients in group 1 the prosthesis separated from its straps because of an early manufacturing

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flaw that was subsequently rectified. One of these patients had a good clinical result but two required removal of the prosthesis. One prosthesis was removed after 2 years because of troublesome dysphagia. The second patient suffered perforation of an unsuspected gastric ulcer a few days after insertion of the device and the prosthesis was then removed.

Two patients in group 2 developed deep sepsis: a retrogastric abscess in one and peritonism with septicaemia in the other. One patient required antrectomy with Roux-en-Y reconstruction for a recurring stricture with heartburn and dysphagia after fundoplication.

Endoscopy. Investigation was performed in 42 patients. The six without follow-up endoscopy all had a good clinical outcome at 1–2 years. The oesophageal mucosa appeared normal in 11 of 22 patients in group 1 and in 13 of 20 in group 2. Grade 3 or 4 oesophagitis was present in two patients in group 1 and in four in group 2.

Consecutive series

Results were good in 101 patients (85 per cent: Visick grade 1, $n = 69$; grade 2, $n = 32$) and poor in 18 (15 per cent: Visick grade 3, $n = 9$; grade 4, $n = 9$). Details of patients with poor results are given in *Table 3*. Control of reflux symptoms with a correctly positioned prosthesis was good: only four of 112 patients with a correctly positioned device had troublesome reflux (Visick grade 3 or 4). None of 22 patients with symptoms of nocturnal choking had recurrence of these symptoms after operation. No patient had gas-bloat syndrome after surgery.

Table 2 *Prospective randomized trial of the Angelchik prosthesis: follow-up at 4–6 years with the number of patients at each Visick grade*

Visick grade		Angelchik (group 1)	Fundoplication (group 2)
1	Good	9	9
2		12	9
3	Poor	2	2
4		2	3
Total		25	23

Table 3 *Details of 18 patients in group 3 with poor clinical outcome after Angelchik prosthesis insertion (Visick grades 3 and 4)*

- Dysphagia ($n = 8$)
  - Prosthesis in thorax ($n = 1$)
  - Prosthesis correctly positioned ($n = 7$)
- Recurrent reflux ($n = 8$)
  - Disruption of prosthesis straps owing to design flaw ($n = 1$)
  - Prosthesis in thorax ($n = 3$)
  - Prosthesis correctly positioned ($n = 4$)
- Vomiting ($n = 1$)
  - Prosthesis slipped down around body of stomach causing obstruction
- Superficial wound pain ($n = 1$)
  - Cause unknown and prosthesis correctly positioned

Dysphagia. Eight patients experienced troublesome dysphagia but only one required reoperation. A further 37 noticed some limitation of swallowing but are symptomless if large food boluses are chewed well (Visick grade 1 or 2).

Complications. There was no 30-day mortality. Morbidity included one patient each with deep vein thrombosis, small pulmonary embolus and incisional hernia. No patient required splenectomy. Details of seven patients in whom the prosthesis migrated are given in *Table 4*. Part of the Angelchik ring was visible in the cardia at endoscopy in one symptomless patient 6 years after surgery.

Endoscopy and histopathology. Macroscopic oesophagitis was noted before operation in 111 of 117 endoscopies but in only 30 of 102 performed at follow-up. Comparative histopathology in the 84 patients with paired preoperative and follow-up biopsies revealed less severe oesophagitis at follow-up in 74 (88 per cent), no change in six (7 per cent) and deterioration in four (5 per cent).

Discussion

All three randomized controlled trials comparing the Angelchik prosthesis with floppy Nissen fundoplication have shown no statistically significant difference between the two procedures[2–4]. The results of the present trial after 4–6 years of follow-up continue to show marginally better results with the Angelchik device. In the other two trials, patients undergoing Nissen fundoplication fared marginally better.

Dysphagia has proved the principal cause of poor results with the Angelchik prosthesis in groups 1 and 3. This is acknowledged as a significant problem with this device[12,13] but preoperative assessment cannot identify those whom it will affect[14]. Assessment of swallowing is crucial to the re-evaluation of the prosthesis. Some limitation of swallowing was noted in 45 of the 119 patients in group 3 but 37 of these 45 were symptomless if they chewed their food well. All 37 patients felt that they had a good result from surgery. Dysphagia occurs frequently after standard Nissen fundoplication[15] but is less common following the floppy procedure[16].

Control of reflux with a correctly positioned prosthesis was excellent with good symptom control and improvement in macroscopic and microscopic oesophagitis. Gas bloat was not a problem with the Angelchik prosthesis but did occur after fundoplication in all three trials. Definition of gas bloat is difficult but Polk[16] reported an incidence of 6 per cent after 312 floppy fundoplications. Prosthesis-related complications were rare despite several reports[13,17–20]. Only six complications were notified to the manufacturers[21] after insertion of 16757 of the new-design prostheses between 1982 and 1987. Migration of the prosthesis from its correct position occurred in 6 per

Table 4 *Details of seven patients in group 3 in whom the Angelchik prosthesis migrated from its correct position*

Patient no.	Prosthesis position	Symptoms	Visick grade	Reoperation	Final clinical outcome
1	Free in abdomen (strap disruption)	Severe reflux	4	Yes	Good
2	Around body of stomach	Vomiting	4	Yes	Good
3	Thorax	Mild reflux	2	No	Good
4	Thorax	Severe reflux	4	Yes	Good
5	Thorax	Mild reflux	2	No	Good
6	Thorax	Severe reflux	4	Yes	Good
7	Thorax	Dysphagia	4	Yes	Poor

cent of patients in group 3 and was associated with both recurrent reflux and dysphagia. Only one symptomless patient in group 3 had evidence of prosthesis erosion into the stomach 6 years after surgery. No patient required splenectomy and there were no operative deaths. Polk[16] reported a 7 per cent incidence of splenectomy after Nissen fundoplication and splenectomy rates as high as 25 per cent have been noted[22].

Surgical placement of the prosthesis appears safe and the ease of insertion may be associated with a lower operative risk, particularly for splenectomy. Very long-term results are unknown. Control of reflux is comparable to that achieved by Nissen fundoplication. Gas bloat can be avoided but dysphagia is certainly more common and in 6 per cent of patients is a major problem. Insertion of the Angelchik prosthesis has been subjected to more scrutiny than any other antireflux procedure, with a national register of cases[23]. There remain no good data on which to condemn the device. It is, however, expensive and saves little operating time[2,4]. The prosthesis is not considered by many to be the operation of choice for reflux control but may remain useful in those whose body habitus makes fundoplication difficult.

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Prognostic significance of cell culture in carcinoma of the oesophagus

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The prognostic significance of the potential of cells to grow in tissue culture was studied in 50 patients with oesophageal cancer. The ability of cell lines to grow from resected oesophageal specimens was determined; from 50 patients, 21 cell lines were established (42 per cent). The patients were divided into two groups on this basis: group 1, from whom cancer cells could be grown as continuous cell lines and group 2, from whom cell lines could not be established. The cumulative survival rate of patients in group 1 was significantly lower than that of those in group 2 (P < 0·05). *There was also a significantly higher incidence of lymph node metastases in group 1* (P < 0·05). *These results suggest that the potential of cancer cells for growth is a useful long-term prognostic indicator for patients with oesophageal carcinoma.*

Few reports have been published on the growth and behaviour of human oesophageal carcinoma cells in culture[1–3]. The use of cell culture techniques has been limited by the low success rate of propagation *in vitro*, in turn limiting clinical application of the method. Establishment of cell lines from tumour tissue samples has been thought to be an indicator of biological malignancy, but this has not been confirmed.

The authors have established 28 oesophageal cancer cell lines from human tumours during the past 5 years; 21 of these were established from 50 consecutive surgical specimens[4]. To evaluate cell culture properties as indicators of biological malignancy, the present study analysed the growth of cell cultures from oesophageal tumours and the clinical outcome of the patients from whom the specimens were taken.

Patients and methods

Data from 50 patients who had undergone resection of oesophageal tumours between 1986 and 1988 were analysed. The patients comprised 37 men and 13 women; their ages ranged from 44 to 79 years. The same operative technique was used in each case and all the patients received postoperative radiotherapy. Each patient's clinical status was classified from stage I to IV using the tumour node metastasis system[5].

Cells from resected oesophageal cancers were cultured as previously described[4] (*Figure 1*). Culture samples were obtained from resected specimens in the operating room. The samples were taken from the mucosal surface and washed four times with minimum essential medium containing 10 μg/ml amphotericin B. Necrotic or haemorrhagic regions, associated muscle and fat were removed. The cancer tissue was minced with sharp scissors into pieces approximately 1 mm in diameter and a crude cell suspension made by forcing the minced tissue through a stainless-steel mesh. The suspension was dispersed into 60-mm cell culture dishes with 6 ml culture medium for primary culture and covered with a 90-mm Petri dish to avoid inversion. Ham's F12–RPMI 1640 medium containing 20 per cent fetal calf serum, 100 units/ml penicillin and 2·5 μg/ml gentamicin was used for primary culture. The cultures were maintained at 37°C in a humidified atmosphere of 5 per cent carbon dioxide in air until confluent.

Cultures were examined daily and the medium usually renewed twice a week. Fibroblast overgrowth was controlled by differential trypsinization and scraping. Initial cell passage was performed when rapid tumour cell growth was observed. After the cells had adapted to culture conditions they were maintained in Ham's F12–RPMI 1640 medium with 2 per cent fetal calf serum. DNA fingerprint analysis showed that each cell line was established individually[4].

DNA ploidy patterns of established cell lines were examined using flow cytometric analysis[6]. Cell nuclei were prepared by treatment with 0·1 per cent pepsin and stained with 50 mg/ml propidium iodide. DNA ploidy patterns were examined using a flow cytometer (EPICS Profile II) and data analysed by cytologic software version 2.0 (both from Coulter, Hialeah, Florida, USA).

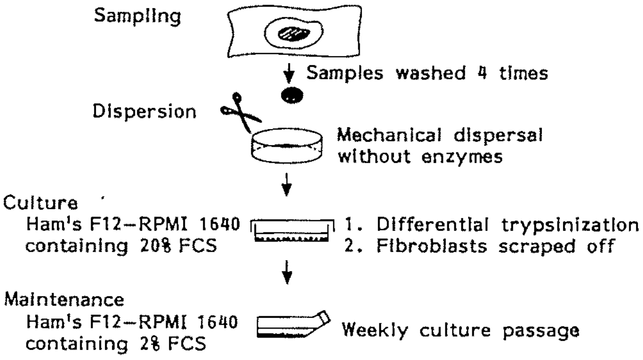
Sampling
Samples washed 4 times
Dispersion
Mechanical dispersal without enzymes
Culture
Ham's F12–RPMI 1640 containing 20% FCS
1. Differential trypsinization
2. Fibroblasts scraped off
Maintenance
Ham's F12–RPMI 1640 containing 2% FCS
Weekly culture passage

Figure 1 *Method for culture of cells from oesophageal tumour specimens. FCS, fetal calf serum*

Statistical analysis

Differences between patient groups were assessed using Fisher's exact test. The cumulative survival curves for patient groups were calculated by the Kaplan–Meier[7] method and compared using the log rank test.

Results

From 50 consecutive resected oesophageal cancer specimens, 21 cell lines were established[4], a success rate of 42 per cent. All of the 21 cell lines were derived from patients with squamous cell carcinoma: in six this was well differentiated, in seven moderately differentiated and in eight poorly differentiated. The growth characteristics of the cell lines have been previously reported[4]. The population doubling time ranged from 13·7 to 75·5 h. Plating efficiencies of the cell lines on plastic ranged between 0·1 and 17·5 per cent. Nine cell lines produced recognizable colonies in soft agarose and seven were tumorigenic in athymic nude mice. The number of chromosomes ranged from 46 to 118.

The patients were then divided into two groups: group 1 ($n = 21$), from whom cancer cells grew continuously in culture and group 2 ($n = 29$), from whom cancer cells failed to grow continuously. Two cell lines (KYSE-240 and KYSE-390) that separated well from fibroblasts and grew at a moderate rate were included in group 1. Unfortunately, these two cell lines were lost. The clinical and pathological backgrounds of the patients are shown in *Table 1*. There were no significant

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Table 1 *Clinical features of patients with oesophageal carcinoma*

	Group 1 ($n = 21$)	Group 2 ($n = 29$)	P‡
Mean(s.d.) age (years)	62·4(9·1)	62·3(9·7)	
Sex ratio (M:F)	14:7	23:6	n.s.
Location of tumour			
Cervical	3	1	n.s.
Upper intrathoracic	1	4	
Middle intrathoracic	11	18	
Lower intrathoracic	6	4	
Abdominal	0	2	
TNM classification			
T_1	1	6	n.s.
T_2	6	4	
T_3	8	16	
T_4	6	3	
N_0	3	15	<0·05
N_1	18	14	
M_0	19	23	n.s.
M_1	2	6	
Stage			
I	0	3	n.s.
IIa	3	9	
IIb	5	2	
III	11	9	
IV	2	6	
Histological type			
Squamous cell carcinoma			
Well differentiated	6	7	n.s.
Moderately differentiated	7	9	
Poorly differentiated	8	9	
Undifferentiated	0	1	
Adenocarcinoma	0	1	
Unknown	0	2	
Preoperative treatment			
Radiation	2	2	n.s.
Chemotherapy*	2	4	
Radiation plus chemotherapy	1	2	
None	16	21	
Operation			
Non-curative	3	3	n.s.
Curative	18	26	
No. of culture dishes†			
≤3	8	12	n.s.
4–6	7	10	
≥7	6	7	

TNM, tumour node metastasis. *Cisplatin; †number used in primary culture. ‡Fisher's exact test; n.s., not significant

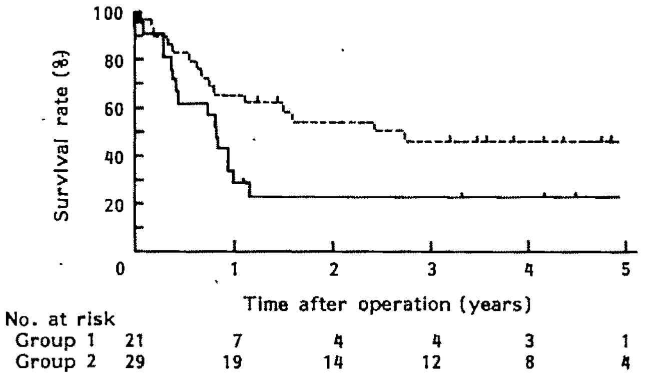

Figure 2 *Cumulative survival curves for patients with oesophageal cancer calculated by the Kaplan–Meier method.* ——, *Patients from whom cell lines were established (group 1);* ——, *patients from whom cell lines were not established (group 2);* ⊥, *censored data.* P < *0·05 (log rank test)*

Table 2 *Time required for first passage of cell lines, DNA ploidy pattern and patient survival*

Cell line	Time for first passage (weeks)	DNA ploidy	Patient survival (months)
KYSE-30	5	Diploid	6
50	10	Aneuploid	4
70	10	Aneuploid	12
110	13	Diploid	4
140	6	Aneuploid	5
150	6·5	Diploid	10
170	7	Diploid	60*
180	2·5	Diploid	1
190	48	Diploid	24†
200	5	Diploid	12
220	3·5	Diploid	12
240	6	—	1
270	9	Aneuploid	9
280	28	—	14
350	24	Aneuploid	5
360	16	—	54*
390	8	—	10
410	4	Aneuploid	48*
450	20	Aneuploid	10
510	2·5	Diploid	5
520	44	—	39*

*Alive; †lost to follow-up

differences between the two groups in sex ratio, age, tumour location, histological stage or type, invasion of the adventitia, preoperative treatment, or the number of culture dishes used.

The cumulative survival curves of the two groups are shown in *Figure 2*. The survival rate of patients in group 1 was significantly lower than that of those in group 2 ($P < 0·05$, log rank test).

A significant difference was also observed between the two groups in the number of patients with lymph node metastases, the incidence of which was higher in group 1 than in group 2 ($P < 0·05$).

The time required for first passage of the cell lines, DNA ploidy pattern and patient survival are shown in *Table 2*. The time for first passage ranged from 2·5 to 48 weeks. There was no significant correlation between the time for first passage and patient survival. DNA ploidy patterns of nine cell lines were diploid and those of seven aneuploid. There was no significant difference between the survival curves of patients with diploid or aneuploid tumours.

Discussion

Various prognostic indicators of oesophageal cancer have been proposed, including DNA index, histopathological type, receptor status, *in vitro* colony growth, and immune reaction[8–12]. Biological staging of the intrinsic malignant potential of the tumour would be useful in determining prognosis. The present study was initiated to evaluate the potential of cell culture in predicting patient survival.

Growth characteristics of cancer cells in tissue culture may reflect the malignant potential of these cells. Previous attempts to correlate growth in culture with tumour behaviour *in vivo* in patients with prostatic carcinoma have yielded inconclusive results[13]. In ovarian[14] and breast[15] carcinoma, the establishment of a satisfactory culture has proven easier for advanced tumours. Cells that adapt and grow well in culture appear to be more aggressive *in vivo*.

In oesophageal cancer, Robinson *et al.*[2,3] demonstrated that the behaviour of cultured core tumour and biopsy samples correlated well with invasiveness *in vivo* and with prognosis; furthermore, they showed that *in vitro* growth behaviour correlated with histopathological differentiation. The authors categorized tumour adaptation in terms of either rapid epithelial cell growth, subculture capability, or continuous cell line establishment. They also concluded that the ability of an oesophageal cancer sample to become successfully established *in vitro* appears to depend on the biological properties of the tumour rather than on the technique of tissue culture. However, they were unable to establish enough cell lines for statistical analysis of prognosis. The present authors have established 21 homogeneous and unique cell lines from 50 consecutive patients[4] with a culture success rate of 42 per cent, higher than previously reported results. The culture techniques used can be summarized as: (1) isolation of tumour cells; (2) disinfection of the surgical specimen; (3) protection from contamination; (4) mechanical cell dispersion without enzymes; and (5) control of fibroblast overgrowth. Cross-contamination of cell lines was eliminated by DNA fingerprint analysis.

Once established, these cell lines were used to analyse the relationship between growth potential *in vitro* and the patient's prognosis. The present study demonstrates that the ability of cells from an oesophageal cancer sample to establish a continuous cell line successfully is a significant prognostic factor. Although this growth property correlated significantly with the incidence of lymph node metastasis, there was no correlation with histopathological differentiation. Of the 21 cell lines established, 13 grew in protein-free medium. Interestingly, the prognosis of the 13 patients from whom they were taken was the poorest of the study group[16] ($P = 0{\cdot}19$). All surgical samples were taken from resected oesophagus, suggesting that the ability of cells to grow continously *in vitro* depends on the characteristics of the primary tumour, not on those of metastatic lesions to the lymph nodes.

In this series, five cancer cell lines grew continuously despite previous cytotoxic therapy; four of the patients from whom these lines were derived died within 10 months of surgery. It would therefore seem that cancer cells that are resistant to cytotoxic therapy exhibit the most aggressive behaviour.

In this study, the time taken for each cell line to reach the earliest passage ranged from 2·5 to 48 weeks. This time, which was expected to be related to prognosis, did not in fact correlate with patient survival. DNA ploidy analysis revealed that diploid as well as aneuploid tumours grew *in vitro*. However, this feature is again not of prognostic significance.

Phase-contrast microscopy revealed that the growth pattern of cancer cells maintained continuously could be either invasive or expansive. These growth patterns may reflect characteristics *in vivo*: it is possible, therefore, that these investigations might be useful in planning oesophageal cancer treatment.

Two problems, however, remain. First, difficulty in obtaining enough cells from preoperative biopsy samples results in a low success rate of cell culture. Second, the time required to establish cell lines is too long for clinical application. Nevertheless, the value of cell culture as a prognostic tool deserves further investigation.

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Prospective randomized study of one- or two-layer anastomosis following oesophageal resection and cervical oesophagogastrostomy

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In a prospective randomized study, one- and two-layer anastomoses were compared following subtotal oesophagectomy and gastric substitution with cervical oesophagogastric anastomosis. After 54 one- and 53 two-layer procedures the rates of anastomotic leakage were the same (19 per cent). After a mean follow-up of 44 weeks, 13 of 51 patients (25 per cent) undergoing one-layer anastomosis and 28 of 50 (56 per cent) having the two-layer procedure complained of cervical dysphagia and required dilatation. The anastomotic strictures were fibrotic in 11 of 51 patients (22 per cent) undergoing one-layer anastomosis and in 24 of 50 (48 per cent) receiving the two-layer operation. Strictures were malignant in two and four patients (4 and 8 per cent) respectively. The lower incidence of fibrotic stricture following one-layer anastomosis was significant ($P < 0{\cdot}01$), but not that of malignant stricture. With comparable leakage rates, one-layer anastomosis is superior to the two-layer procedure because of the lower incidence of fibrotic stricture.

Transthoracic or transhiatal resection of the oesophagus and its replacement by the stomach is the standard procedure in surgical treatment of oesophageal carcinoma. Two frequent complications are leakage and late stricture of the oesophagogastric anastomosis. In a previously published literature review[1] of 59 series a mean leakage rate of 15 per cent was reported following gastric replacement of the oesophagus. When the anastomosis was placed in the neck following a transhiatal or three-phase McKeown-type resection[2], leakage rates were significantly higher than with intrathoracic localization of the anastomosis following a two-phase Lewis procedure[3]. The mortality rate associated with leakage was more than three times higher in thoracic than cervical anastomoses (70 *versus* 20 per cent).

Life expectancy is limited in most patients with resectable oesophageal carcinoma because of the advanced stage of disease. Good palliation with rapid and lasting relief of dysphagia is the major goal of surgery. The development of anastomotic stricture reduces the benefit of the operation and casts doubt on the utility of palliation.

The high complication rate of oesophagogastric anastomosis may be caused by the lack of serosa in the oesophagus and the reduced blood supply to the anastomotic region[4]. The suture material or technique is decided by the operating surgeon but most use absorbable and atraumatic sutures for gastrointestinal anastomosis. The best technique for oesophagogastric anastomosis is still controversial and numerous methods have been described. The low leakage rate reported by Akiyama[5] using a two-layer technique led to this method being used at the University of Cologne since 1983. One-layer anastomosis is used in other parts of the gastrointestinal tract, and a report[6] of the International Organisation for Statistical Studies on Diseases of the Esophagus (OESO) showed promising results for one-layer oesophagogastric anastomosis. One- and two-layer oesophagogastric anastomoses were, therefore, compared in a prospective randomized study.

Patients and methods

The study was designed as a phase 2 prospective randomized trial[7] with anastomotic leakage and late stricture as endpoints. All patients presenting with resectable squamous cell carcinoma of the oesophagus over a 3-year period (1988–1990) were included. If the carcinoma was resectable and the stomach suitable for oesophageal replacement, the type of anastomosis was randomly assigned during operation, following the guidelines of the Helsinki declaration[8] and the local ethical committee. Surgery was performed by two surgeons with extensive experience in oesophageal procedures.

Anastomotic leakage was defined as any radiographically demonstrable extravasation of water-soluble contrast medium at the site of the anastomosis on day 7 after operation.

Anastomotic stricture was defined as any form of cervical dysphagia in the anastomotic region requiring endoscopic dilatation or operative revision. This subjective clinical measure was used because a previous pilot study showed that the radiographically measured width of the anastomosis correlates poorly with ability to swallow.

Surgical technique

A gastric tube was created by resection of the lesser curvature. Following transthoracic resection and palliative transhiatal resection the tube was placed retrosternally and following 'curative' transhiatal dissection retromediastinally. All anastomoses were performed with monofilament absorbable synthetic suture material (4/0 polydioxanone) and an atraumatic needle.

Two-layer anastomosis (Figure 1a).The outer layer was performed with interrupted sutures, which were passed through the muscularis of the oesophagus and the seromuscularis of the stomach. The inner mucosal layer was sutured continuously, ensuring that submucosa apposed submucosa.

One-layer anastomosis (Figure 1b). A continuous suture was passed through all layers of the oesophagus and stomach using the technique described by Gambee[9].

On day 7 after operation a water-soluble contrast study was carried out in all patients; if no leakage was detected, increasing oral nutrition was started. If anastomotic leakage was shown, parenteral nutrition or distal tube feeding was continued and the contrast study was eventually repeated.

Patients with advanced tumours and those undergoing palliative resection received postoperative radiotherapy to include the supraclavicular fossae and the anastomotic region for tumours of the upper third of the thoracic oesophagus and the coeliac region for tumours of the mid and lower thoracic thirds.

Follow-up was carried out at intervals of 3 months and included

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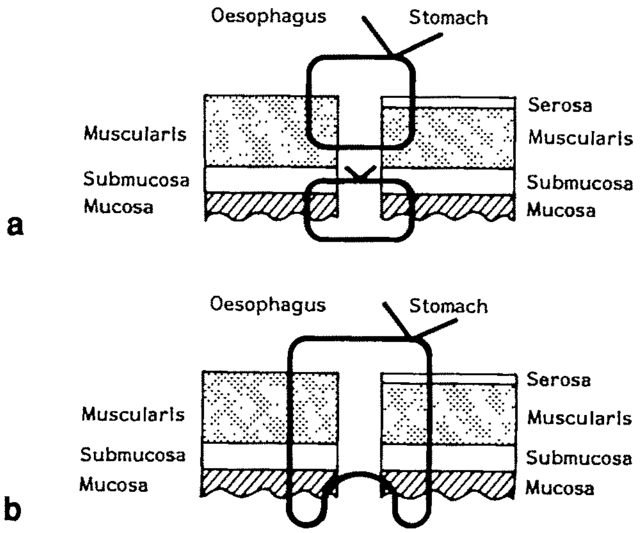

Figure 1 *Technique of* **a** *two-layer and* **b** *one-layer oesophagogastric anastomosis*

clinical examination, contrast studies, upper gastrointestinal endoscopy and a standardized interview about eating habits and swallowing ability. If a patient complained of cervical dysphagia, computed tomography, endosonography and biopsy of the anastomosis were carried out. In those with an anastomotic stricture, endoscopic dilatation to 16 mm was performed[10].

Statistical analysis

Quantitative data were compared using Student's unpaired t test and qualitative data by χ^2 analysis. The risk of developing a benign anastomotic stricture was calculated by the method of Kaplan and Meier[11] and compared using the log rank test. $P < 0.05$ was considered significant.

Results

Fifty-four patients underwent one-layer anastomosis and 53 the two-layer procedure. The groups were comparable regarding patient characteristics (*Tables 1* and *2*). The hospital mortality rate was 6 per cent. The causes of death were pulmonary failure in three patients, cardiac failure in two and pulmonary embolism in one. None of the deaths was caused by a complication of anastomosis.

Anastomotic leakage (*Table 3*) was observed in ten patients in each group. Two leaks following one-layer anastomosis and three following the two-layer procedure were asymptomatic and detected only by radiography. A salivary fistula developed in three patients with one-layer anastomosis and in four with two-layer anastomosis. Cervical abscess formation required incision and drainage in two patients following the one-layer procedure. All leaks healed spontaneously within a mean(s.d.) of 20(3) days (one-layer) and 16(4) days (two-layer) after operation.

Factors such as sex, age, weight, concomitant metabolic disease (diabetes), cirrhosis, cardiac and pulmonary disorders, tumour stage, operative procedures (transmediastinal *versus* transthoracic approach, curative *versus* palliative resection), surgeon, blood loss, operating time, duration of mechanical ventilation and the incidence of other postoperative complications did not have a significant influence on the leakage rate.

At discharge, a mean(s.d.) of 17(7) days after surgery, 30 patients with one-layer (59 per cent) and 33 patients with two-layer (66 per cent) anastomosis were able to eat normal meals. Soft diet was tolerated by 19 patients (37 per cent) following one-layer and 16 (32 per cent) after two-layer anastomosis. Three patients (one-layer anastomosis, two; two-layer anastomosis, one) were discharged soon after closure of an anastomotic leak.

All patients completed at least 6 months of follow-up. Twelve patients undergoing one-layer and 25 undergoing two-layer anastomosis complained of cervical dysphagia within 6 months of operation. These stenoses were dilated successfully, except in one patient who had undergone the one-layer procedure and required surgical correction.

Including patients who underwent dilatation, 91 per cent of all patients with one-layer and 83 per cent with two-layer

Table 1 *Patient characteristics, type of operation, surgeons and adjuvant treatment in the two groups*

	Type of anastomosis	
	One-layer	Two-layer
Patients		
No.	54	53
Mean(s.d.) age (years)	59(9)	57(8)
Sex ratio (M:F)	40:14	45:8
Type of resection*		
Transthoracic	11 (20)	13 (25)
Transhiatal	43 (80)	40 (75)
Route of reconstruction*		
Retromediastinal	36 (67)	31 (58)
Retrosternal	18 (33)	22 (42)
Surgeon no.*		
1	20 (37)	21 (40)
2	34 (63)	32 (60)
Adjuvant treatment*		
None	34 (63)	31 (58)
Postoperative radiotherapy	17 (31)	19 (36)

*Values in parentheses are percentages

Table 2 *Postoperative complications, leakage and hospital mortality following one- or two-layer oesophagogastric anastomosis*

	Type of anastomosis	
	One-layer ($n = 54$)	Two-layer ($n = 53$)
Postoperative complications		
None	27 (50)	30 (57)
Pleural effusion	12 (22)	9 (17)
Recurrent laryngeal nerve injury	10 (19)	8 (15)
Pneumonia or respiratory insufficiency	7 (13)	6 (11)
Severe arrhythmia or cardiac insufficiency	10 (19)	13 (25)
Other	8 (15)	7 (13)
Anastomotic leakage	10 (19)	10 (19)
Hospital mortality	3 (6)	3 (6)

Values in parentheses are percentages

Table 3 *Leakage following one- or two-layer oesophagogastric anastomosis*

	Type of anastomosis	
	One-layer	Two-layer
Anastomotic leakage*		
All	10 of 54 (19)	10 of 53 (19)
Requiring operative revision	2 of 10 (20)	0 of 10 (0)
Type of resection*		
Transthoracic	2 of 11 (18)	2 of 13 (15)
Transhiatal	8 of 43 (19)	8 of 40 (20)
Route of reconstruction*		
Retromediastinal	4 of 36 (11)	3 of 31 (10)
Retrosternal	6 of 18 (33)	7 of 22 (32)
Surgeon no.*		
1	3 of 20 (15)	4 of 21 (19)
2	7 of 34 (21)	6 of 32 (19)
Mean(s.d.) duration of healing (days)	20(3)	16(4)

*Values in parentheses are percentages

Table 4 *Anastomotic strictures following one- or two-layer oesophagogastric anastomosis*

	Type of anastomosis		
	One-layer	Two-layer	*P*
Type of stricture*			
Fibrotic	11 of 51 (22)	24 of 50 (48)	<0·01
Malignant	2 of 51 (4)	4 of 50 (8)	n.s.
Mean(s.d.) time of appearance after operation (weeks)			
Fibrotic	9(5)	10(6)	n.s.
Malignant	25(16)	21(9)	n.s.
Previous anastomotic leak*	5 of 10 (50)	8 of 10 (80)	n.s.
Type of resection*			
Transthoracic	2 of 9 (22)	4 of 12 (33)	n.s.
Transhiatal	11 of 42 (26)	24 of 38 (63)	<0·01
Route of reconstruction*			
Retromediastinal	7 of 36 (19)	15 of 31 (48)	<0·05
Retrosternal	6 of 18 (33)	13 of 22 (59)	<0·05
Surgeon no.*			
1	5 of 18 (28)	13 of 20 (65)	<0·05
2	8 of 33 (24)	15 of 30 (50)	<0·05
Adjuvant postoperative radiotherapy*			
With	6 of 17 (35)	11 of 19 (58)	n.s.
Without	7 of 34 (21)	17 of 31 (55)	<0·01
Mean(s.d.) no. of dilatations	3·1(1·7)	2·7(1·4)	n.s.

*Values in parentheses are percentages. n.s., Not significant

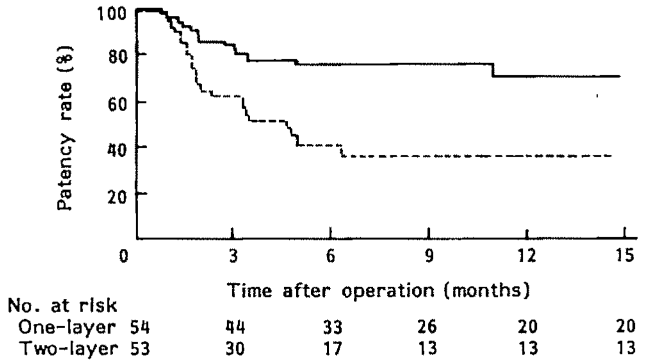

Figure 2 *Risk of developing a fibrotic stricture following one-layer (——) or two-layer (-----) oesophagogastric anastomosis.* P < 0·05 *(log rank test)*

anastomosis were able to eat solid meals 6 months after operation.

At the time of analysis 24 patients with one-layer and 27 with two-layer anastomosis had died from recurrent oesophageal cancer after a mean(s.d.) of 44(30) and 40(26) weeks respectively. Twenty-seven patients with the one-layer and 23 with the two-layer procedure remain alive at a mean(s.d.) of 42(40) and 48(31) weeks respectively.

The overall number of strictures was 41 (*Table 4*). Two malignant stenoses occurred following one-layer anastomosis and four after the two-layer procedure. When comparing both groups, the frequency of fibrotic stricture was significantly lower ($P < 0{\cdot}01$) following one-layer anastomosis. Patients with fibrotic stricture suffered earlier from dysphagia than those with malignant stenosis. The frequency of stricture increased in each group following retrosternal placement of the stomach, previous anastomotic leak and postoperative radiotherapy. When the radiation field was extended to the anastomotic region the incidence of stricture was higher in both groups (one-layer anastomosis, three of five patients; two-layer anastomosis, three of four) than when the field did not include this region (three of 12 and eight of 15 respectively).

The number of endoscopic dilatations was similar in both groups; three patients in each underwent more than four dilatations. The risk of developing a fibrotic stricture during the first year after operation (*Figure 2*) was 30 per cent for one- and 64 per cent for two-layer anastomosis ($P < 0{\cdot}05$).

Discussion

Owing to the lack of controlled clinical studies, assessment of the best technique for oesophagogastric anastomosis is difficult. In a literature review[1] neither one- or two-layer nor manual or mechanical anastomosis was found to have a significant influence on leakage rates. In the present study leakage rates with one- and two-layer anastomosis were similar and in agreement with those found in a literature review[1] and those reported by the Association Française de Chirurgie[12] and the OESO study group[6]. This result, however, is not satisfactory. Substantially lower rates have been achieved, and the rate at the University of Cologne was 5 per cent lower at the beginning of the study. The special interest in detection of minor leakage during the present study is probably responsible for the increased rate. The rate would be around 5 per cent lower in both groups (one-layer anastomosis, 15 per cent; two-layer anastomosis, 13 per cent) if completely asymptomatic leaks were excluded, and around 10 per cent lower (9 and 8 per cent respectively) if only clinically significant leaks were included. With both techniques, leakage rates were higher following retrosternal placement of the gastric tube. The length of the oesophageal substitute (greater for the retrosternal than retromediastinal route) correlates with the leakage rate.

Fibrotic strictures were half as frequent following one- than two-layer anastomosis, perhaps because the loss of lumen, disturbance of blood supply and scar formation were lower with the one-layer procedure[13]. Previous leakage, retrosternal reconstruction and postoperative radiation increased the risk of stricture formation in both groups. Following retrosternal reconstruction and postoperative radiation this increase was higher with one-layer than two-layer anastomosis. Owing to the small number of fibrotic strictures following one-layer anastomosis, a definite evaluation of this observation was not possible.

Even for one-layer anastomosis the risk of developing a stricture after 1 year was relatively high (30 per cent). The incidence of stricture is influenced considerably by its definition and the quality of follow-up. The definition of stricture in this study was based on the subjective sensation of the patient. Since cervical dysphagia was not very marked in some patients, and disappeared after a single bougienage, the observed stricture rate would be lower if an objective definition were used, although the difference between the two groups would remain unchanged. Reported stricture rates[14–18] vary between 0 and 28 per cent. Orringer and Stirling[19] used the same definition of anastomotic stricture as the present study and reported a comparable rate (37 per cent) of intermittent cervical dysphagia necessitating occasional dilatation and a 15 per cent rate of more persistent dysphagia following cervical oesophagogastrostomy.

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Paper accepted 22 October 1992

Announcement

Association of Surgeons in Training (ASIT)

Membership of the Association is open to all trainees in every surgical specialty. Applicants should hold either the FRCS or CSIG Diploma.

The Association represents the views of members on all matters relevant to surgical training both at national and regional level and has representatives on most of the committees and boards that administer surgical training. Membership is free.

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R. J. Baigrie
Honorary Secretary
Association of Surgeons in Training

Br. J. Surg. 1993, Vol. 80, May, 612–613

Subtotal splenectomy with a microwave coagulator

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A microwave coagulator (Heiwa Electronic, Osaka, Japan) with a frequency of 2450 MHz has been used to perform hepatectomy[1,2] and may also have some application in splenic surgery[2,3]. Use of the coagulator in 17 patients undergoing splenic surgery is reported.

Surgical technique

Of 17 patients undergoing splenic surgery, 13 suffered from liver cirrhosis with marked splenomegaly and hypersplenism, one underwent partial splenectomy for a benign tumour in a spleen of normal size, one with a hepatoma had splenic tissue excised during hepatic surgery to obtain lymphatic cells for adjuvant immunotherapy, and two had splenic trauma. All patients received perioperative antibiotics.

In general, the splenic artery and vein, along with two or three of the main large branches emerging adjacently at the hilum, were preserved; the other hilar vessels were transected. After vessel transection, ischaemic areas of spleen could be distinguished from viable tissue. A resection line was then planned on the remaining viable spleen so as to leave a remnant of 150–300 g, or approximately one-fifth to one-third of the original size. To prevent injury from overheating, the coagulation zone was placed at least 4 cm from the preserved hilar vessels. Coagulation was started on one edge of the spleen. A coagulating probe 0·8 mm in diameter and 3–5 cm in length was completely inserted into the spleen from the diaphragmatic to the visceral surface (*Figure 1*). Power of 80 W was applied for 50 s. A section of spleen approximately 1 cm in diameter was gradually coagulated. A dissociation procedure was necessary to enable withdrawal of the probe. A series of insertions 5 mm from the coagulated area was made along the resection line. Any bleeding from the insertion hole was stemmed by further coagulation or by simple pressure. For the thicker spleen, additional coagulation from the reverse side was necessary (*Figure 1*).

After completion of coagulation, resection was performed with a surgical scalpel through the coagulated zone. The cut splenic surface was generally blood-free except for that from vessels larger than 3 mm in diameter. Digital compression from both surfaces of the proximal spleen was used to assist haemostasis of these vessels, after which they were secured by ligation or suture. Bleeding from insufficiently coagulated areas was stemmed using a short microwave coagulator probe with or without deep insertion. This method was also used for haemostasis and debridement of traumatized spleens. The splenic remnant was replaced in the splenic bed without tension or torsion. A soft tube drain was placed beneath the splenic remnant.

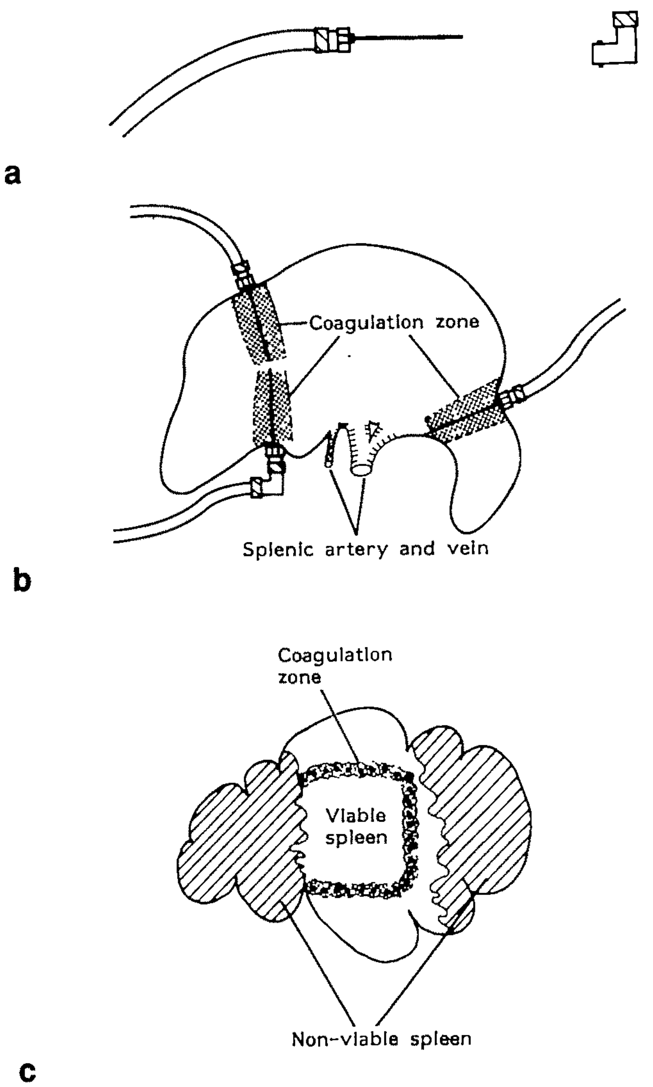

Figure 1 *Subtotal splenectomy for splenomegaly by microwave coagulation.* **a** *Coagulator probe with coaxial cable and right-angled adaptor.* **b** *Insertion of the probe for coagulation from the diaphragmatic surface and with the right-angled adaptor from the visceral surface.* **c** *Zone of coagulation*

Results

Haemostasis achieved using the microwave coagulator on the viable, normal or hypertensive spleen was satisfactory. Mean(s.d.) blood loss during resection of the splenic parenchyma was 292(161) ml for the 13 patients with portal hypertension, < 100 ml for the further two patients with no splenic trauma and minimal for those with trauma. There was no significant postoperative haemorrhage from the splenic remnant, although a splenic hilar vessel tear did occur in one patient. In patients with marked splenomegaly, pyrexia around 38°C and a slight rise in liver transaminase levels occurred after surgery and lasted about 1 week. Three patients died in hospital: one from a complication of cirrhosis 34 days after operation and two from hepatorenal syndrome on days 7 and 21.

Follow-up for 11 surviving patients with cirrhosis was between 7 and 35 (mean 20·2) months. Their general condition was good. The whole blood profile (including platelet count) and liver function were normal. The splenic remnants were studied by ultrasonography and scintigraphy, which showed a good blood supply with no change in size.

In conclusion, the microwave coagulator is a useful tool for parenchymal haemostasis in a variety of splenic salvage operations, particularly where the spleen has an intact blood supply.

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Case report

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Spontaneous rupture of the spleen secondary to metastatic carcinoma

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Spontaneous rupture of the spleen is a relatively rare clinical entity occurring in the normal organ as well as that affected by diseases such as infectious mononucleosis, malaria, typhoid, splenic cyst and leukaemia. Spontaneous rupture of the spleen secondary to metastatic carcinoma is exceedingly rare, only six cases having been reported[1]. The primary sites in these patients were the urinary bladder, stomach, skin (malignant melanoma), liver and lungs. The present case report is believed to be only the second of spontaneous rupture of the spleen following metastatic lung cancer.

Case report

A 58-year-old man was admitted with sharp constant lower abdominal pain aggravated by movement. There was no relevant medical history. On examination the patient was pale; the heart rate was 60 beats/min and blood pressure 130/70 mmHg. There were no signs of external injury and no history of trauma. Physical examination revealed lower abdominal tenderness with mild guarding. Blood tests gave a haemoglobin level of 11·6 g/dl, a white blood cell count of $11{\cdot}7 \times 10^9$/l and a platelet count of 310×10^9/l. Urea, electrolyte and amylase levels were normal. Initial management was conservative.

The next day the patient's general condition deteriorated suddenly and the haemoglobin level fell to 8 g/dl. Ultrasonography demonstrated a ruptured spleen with free fluid in the peritoneum. Chest radiography showed hyperinflated lung fields and some right upper and lower lobe atelectasis, suggesting a possible right hilar obstructing neoplasm.

The patient was resuscitated and an exploratory laparotomy performed. A large amount of free blood and a very large splenic haematoma were found. The spleen was removed. No other abnormality was detected. The postoperative period was uneventful and the patient was allowed home 7 days after operation.

The spleen weighed 1250 g and contained a pale-rimmed centrally cystic lesion 1·5 cm in diameter. Microscopic examination revealed a keratinous moderately well differentiated squamous carcinoma that was probably metastatic from a bronchial lesion. The tumour showed substantial growth around the blood vessels and seemed to be the cause of the haemorrhage.

Some 2 weeks later the patient began vomiting and developed slurred speech, diplopia, mild expressive aphasia and right-sided hemiparesis. Computed tomography demonstrated a cystic tumour in the left fronto-opercular area. A second chest radiograph revealed a hilar lesion on the right side. The patient died 8 weeks later.

Discussion

Carcinomatous metastasis to the spleen is comparatively rare[2]. In routine autopsy series only 0·3–9 per cent of cases are found to have splenic involvement[3]. Warren and Davis[4] have suggested that splenic metastasis usually occurs late in the disease process during widespread tumour dissemination. Instances of solitary splenic metastasis are very rare.

Carcinoma of the breast and lungs is the primary lesion in 30–67 per cent of all splenic metastases[2]. Other primary sites include the pancreas, large intestine, stomach, ovaries and skin (melanoma). Most splenic metastases are the result of haematogenous spread[2].

The present case is believed to be only the second instance of spontaneous rupture of the spleen following metastatic lung disease. Unlike the previous case[5], the patient did not exhibit any symptoms associated with the primary lesion. Onset of splenic rupture was acute. The mechanism of rupture also differed in that substantial tumour growth occurred around the blood vessels, causing spontaneous haemorrhage. There was no evidence of splenic infarction in contrast to the description by Karakousis and Elias[6].

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Rectus repair for midline ventral abdominal wall hernia

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Recurrence-free repair of midline ventral abdominal wall hernia continues to elude surgeons, despite the abundance of described techniques. Based on the observation that spontaneous herniation through the rectus abdominis muscles is unknown, a new technique of repair was devised. The rectus muscles and their sheaths on either side of the hernial defect are directly brought together to obliterate the hernia, the intervening linea alba and intact hernia sac being 'keeled' into the abdominal cavity. Using this technique, 85 consecutive midline abdominal hernias were repaired over an 11-year period. Follow-up was from 18 months to 12 years; there was one recurrence. The rectus repair is recommended as an effective method of dealing with ventral midline abdominal wall hernia.

Midline ventral abdominal wall hernia is a common problem in general surgery, but no definitive repair for this condition is acknowledged as recurrence rates of over 30 per cent[1] are reported. Although numerous techniques of repair have been practised over the past century, all employ approximation of the linea alba or rectus sheath (not muscle) to obliterate the hernial defect. However, in many spontaneously occurring hernias the linea alba itself is a very weak layer so that divarication of the rectus muscles, fatty hernia of the linea alba, and paraumbilical hernia all occur *de novo* through defects of this fibroaponeurotic band. Spontaneous herniation through the rectus abdominis, however, is virtually unknown. Thus, the logical repair for ventral midline abdominal wall hernia would be to approximate the rectus muscles in the midline, allowing no linea alba to intervene between them.

Such a repair has been used in this unit since 1978. Paraumbilical, umbilical, epigastric and midline incisional hernias were regarded as suitable for this 'rectus repair', since the underlying weakness, a defect in the linea alba, is common to all of them. The technique of repair and experience with it are presented.

Patients and methods

All adult patients presenting for surgery with midline ventral abdominal wall hernia from 1978 to 1989 underwent repair by the method described below. Their ages ranged from 25 to 72 years; there were 71 women and 14 men. Of 85 hernias repaired, 44 were paraumbilical, 23 incisional, 11 umbilical and seven epigastric.

Through an appropriately placed incision, depending on the type of hernia, the sac was dissected down to its neck and freed from the linea alba extraperitoneally. The subcutaneous fat was mobilized from the hernia sac and dissection extended laterally for a distance of at least 3 cm from the medial edge of the rectus abdominis (not linea alba). The sac and linea alba were inverted and no attempt made to dissect sac contents. Repair was commenced with the left index finger (of a right-handed surgeon) inserted into the hernial defect extraperitoneally (*Figure 1*). This served two purposes: it ensured that the tissue taken by the suture included a generous full-thickness bite of the medial border of the rectus muscle and sheath, and it also aided in guiding the needle through an extraperitoneal course, ensuring that no underlying viscus was penetrated. An inverting suture technique was used, starting about 5 cm above the hernia and extending approximately the same distance below. Sutures were placed 2–3 cm

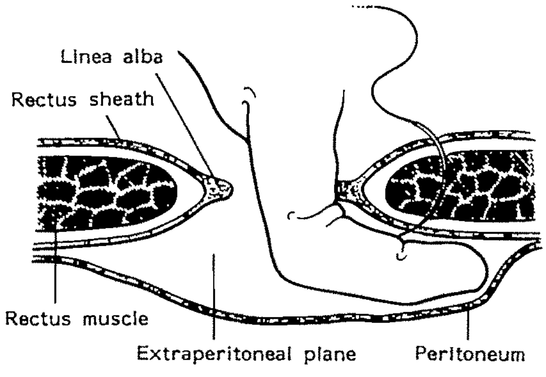

Figure 1 *Index finger guiding needle through the full thickness of the rectus abdominis muscle and sheath in the extraperitoneal plane*

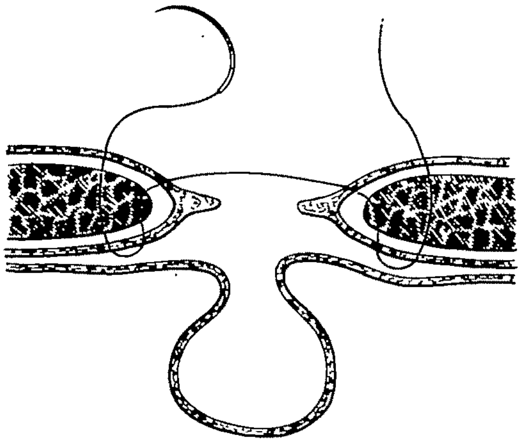

Figure 2 *Suture placement*

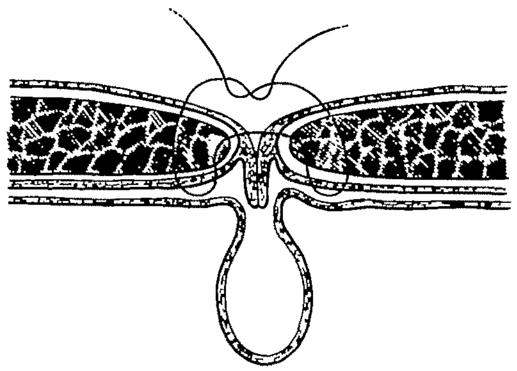

Figure 3 *Rectus muscles approximated in midline with 'keeling' of linea alba into the abdomen*

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laterally to the medial border of the rectus, exiting medially to the border of the rectus on the same side. The needle then entered the medial edge of the rectus on the opposite side and exited 2–3 cm laterally through the muscle (*Figure 2*). Longitudinally, suture placement was no more than 1 cm apart. Suture-line tension was made just sufficient to approximate the tissues. The effect of this suturing technique was to bring the muscle bellies of the rectus muscles together in the midline to close the hernial defect, while inverting the hernia sac and potentially weak linea alba in 'keel' fashion into the abdominal cavity (*Figure 3*).

With small hernias, the last one or two sutures were placed by relaxing the tension on the suture line, allowing the left index finger to remain in position. With large defects, two lengths of suture from opposing ends were used. This served two purposes. First, the widest part of the defect, its centre, was gradually narrowed by the opposing sutures, eliminating undue stress on both suture and tissues. Second, the last sutures could be placed under direct vision since the edges of the rectus muscles and sheath were already raised as ridges by sutures from cephalad and caudad ends of the repair.

A continuous suture of 0 loop nylon was used routinely. Good haemostasis was generally achieved but, in large hernias requiring extensive mobilization of fat, a subcutaneous suction drain was used. Skin edges were approximated with a subcuticular suture. General anaesthesia with muscle relaxation was employed in all cases.

Results

Follow-up was routinely performed at 6 and 18 months after operation and all patients were reviewed for the purpose of this study. Follow-up was for a mean of 71 months (range 18 months to 12 years). There was one recurrence (1 per cent), which was detected at 18-month follow-up. At reoperation this was attributed to technical error, since the suture line was found intact but not engaging the rectus muscle on one side. This patient remains well 18 months following the second operation.

Discussion

The recurrence-free repair of midline ventral abdominal wall hernia continues to challenge the general surgeon, despite the abundance of described techniques. Although prolonged tissue support while fascial healing takes place[2] and proper suture placement[3] have contributed in the recent past towards reducing recurrence, this continues to occur with an incidence of over 30 per cent[1]. The widespread use of non-absorbable suture material has significantly reduced the incidence of incisional hernia[4,5] and virtually eliminated suture failure as a cause of recurrent herniation. This is demonstrated at surgery for recurrence, when an intact suture line is almost invariably found displaced to one side of thin attenuated tissue, which forms the edge of the hernia sac. Tissue failure is the major cause of hernia recurrence.

The common principle underlying all currently employed methods of repair is approximation of the fibroaponeurotic linea alba or anterior rectus sheath. The concept of muscular approximation described in the present paper is a marked deviation from this tradition; the integrity of the repair depends on the natural strength of the rectus abdominis and its sheath. Muscle is dynamic tissue capable of maintaining an isometric state with varying levels of load. The linea alba, however, is fibrocollagenous and lacks this ability, so that over a period of time with altering levels of load it becomes stretched beyond its elastic limit, predisposing to herniation. The relative weakness of the linea alba is underlined by the fact that incisional hernia occurs most commonly after midline incisions, while herniation through muscle-cutting abdominal incisions is much less common[1]. In fact the incidence of incisional hernia is increased after transverse abdominal incisions when they extend on to the midline[1]. Since the rectus repair inverts the linea alba, removing it from the plane of the anterior abdominal wall, all potentially weak tissue is avoided.

Current surgical teaching dictates that suture placement should be at least 1 cm from the wound edge when closing a midline abdominal incision[6]. This empirical distance is not useful since a thin attenuated linea alba can be several centimetres wide in some patients. A more important principle should be to insert the suture into the medial edge of the rectus abdominis muscle. In the obese or multiparous patient with divarication of the rectus muscles, the distance of the rectus from the wound edge would be considerably more than 1 cm, thus larger bites of tissue would be necessary to approximate the muscles in the midline.

The vertical nature of the repair is critical to its integrity. In transverse repairs, such as in the Mayo[7] technique, separation of the rectus muscles is increased and linea alba is used for the repair. These two factors in combination may predispose to hernia recurrence in the space between the rectus muscles.

Soliman's good results[8], we believe, derive not from the number of layers involved in repair, but because the method used is the only technique that directly engages the rectus muscles from both sides. However, the approximating technique does not ensure that the muscles are closely apposed with no intervening linea alba. In addition, dissecting the contents of the hernia sac and mobilizing the adjacent intraperitoneal structures can be time consuming and bloody. Since the rectus repair is entirely extraperitoneal, tedious intraperitoneal dissection is avoided; ileus occurred in no patient in the present series. Although sac inversion has been objected to on grounds of predisposing to mechanical bowel obstruction, this complication has never been encountered and it is more likely to be a theoretical concern than a practical one[9]. Since the present method achieves 'keeling' of the hernia sac by one layer of suture, it is carried out more quickly than by the traditional Maingot[10] technique using several layers of sutures.

The efficacy of rectus repair is demonstrated by the fact that during 11 years of practice there was only a single recurrence and even this was entirely avoidable as it arose through a failure of technique. This repair is recommended for widespread adoption.

Acknowledgements

Figures 1–3 were drawn by Gillian Lee.

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Incidence of haemorrhoids and anorectal varices in children with portal hypertension

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A prospective study of 60 children with portal hypertension showed a significant incidence of haemorrhoids (33 per cent), anorectal varices (35 per cent) and external anal varices (15 per cent). Four children (7 per cent) complained of anorectal symptoms. A comparison of extrahepatic with intrahepatic disease showed that the former was associated with a higher incidence of both haemorrhoids and anorectal varices (57 versus *26 per cent and 64* versus *26 per cent respectively). The occurrence and severity of haemorrhoids was related to the number of previous oesophageal sclerotherapy sessions* (P = *0·001). Problems relating to anorectal pathology were unusual, but treatment with haemorrhoidal sclerotherapy or banding was satisfactory for the symptomatic patients.*

The occurrence of oesophageal varices in children with portal hypertension is well recognized[1,2], but observations of associated anorectal abnormalities have been few. Haemorrhoids and anorectal varices are prevalent[3,4] in adults with portal hypertension, but rarely produce gastrointestinal bleeding[5–11]. Hosking *et al.*[3], for example, found that among adults with cirrhosis up to 40 per cent had anorectal varices and 25 per cent haemorrhoids. A retrospective study[12] of 189 children with portal hypertension revealed a combined incidence of symptomatic anorectal varices and haemorrhoids of 4·7 per cent. A prospective study was undertaken to investigate the incidence of symptomatic and asymptomatic anorectal problems and determine possible aetiological factors.

Patients and methods

Sixty consecutive children with portal hypertension (endoscopic evidence of oesophageal varices and/or splenomegaly) undergoing upper gastrointestinal tract endoscopy between December 1990 and October 1991 were examined by proctoscopy for anorectal abnormalities. Anorectal symptoms such as fresh rectal bleeding, anal pain or prolapse were recorded before examination. The aetiology of portal hypertension, patient age, grade of oesophageal varices at first endoscopy and number of sclerotherapy sessions were recorded. Liver function (bilirubin, alkaline phosphatase and aspartate aminotransferase levels), haemoglobin concentration and platelet count at the time of examination were noted. Upper gastrointestinal tract endoscopy and proctoscopy were performed under general anaesthesia with appropriate parental or guardian consent.

Characterization of anatomical abnormalities of the anorectal region was based on the definitions used by Hosking *et al.*[3]. An external haemorrhoidal complex consisted of small superficial blue veins <2 mm in diameter that became engorged on gentle anal traction. External anal varices were superficial veins ⩾2 mm in diameter that could be emptied by gentle compression, but which refilled immediately. Anal canal and rectal varices were recognized as discrete submucosal blue or slate-grey veins. Haemorrhoids were distinguished from anorectal varices by the appearance of purple-red vascular cushions in the lower anal canal that prolapsed into the lumen of the proctoscope. A simple grading scheme (I–III) was used to assess the severity of each feature; each grading was agreed by two observers.

Results are expressed as median (range). Initial analysis of categorical data was performed by the χ^2 test with Yates' correction for continuity. Intergroup comparisons were made and associations assessed non-parametrically using the Mann–Whitney *U* test and Spearman rank correlation coefficient (r_S) respectively. $P < 0{\cdot}05$ was considered significant.

Results

Patients

There were 21 boys and 39 girls of median age 7·5 years (range 10 months to 18 years). Portal hypertension was caused by cirrhosis or intrahepatic fibrosis in 46 children of median age 7·5 years (range 10 months to 18 years) and by extrahepatic portal vein occlusion in 14 with a median age of 10 (range 4–15) years (*Table 1*). The difference in age between the two groups was not significant ($P = 0{\cdot}13$). Forty-four patients (73 per cent) had presented with gastrointestinal bleeding, two were undergoing investigation for jaundice and two for anaemia and splenomegaly. Twelve children (20 per cent) with extrahepatic biliary atresia treated by Kasai portoenterostomy were examined as part of follow-up. These children had clinical evidence of portal hypertension such as splenomegaly and oesophageal varices, but did not have a history of gastrointestinal bleeding.

All 27 children with extrahepatic biliary atresia had undergone portoenterostomy and a further eight other surgical procedures including laparotomy for gastrointestinal bleeding, splenectomy, and splenectomy with oesophageal transection.

Forty-four children with bleeding from oesophageal varices were treated by injection sclerotherapy. The median number of sessions of sclerotherapy before the current examination was 6 (range 1–17) over a period of 1 month to 9 years. All these children had endoscopically proven oesophageal varices.

Anorectal findings

On external examination, 44 children (73 per cent) had an abnormal external haemorrhoidal plexus; nine (15 per cent) of

Table 1 *Aetiology of portal hypertension*

	No.
Extrahepatic portal hypertension	
Portal vein occlusion	14
Intrahepatic portal hypertension	
Extrahepatic biliary atresia after portoenterostomy	27
Idiopathic cirrhosis	4
Congenital hepatic fibrosis	4
Cystic fibrosis	4
α_1-antitrypsin deficiency	2
Alagille's syndrome	2
Sclerosing cholangitis	2
Gaucher's disease	1
Total	46

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Table 2 *Symptomatic anorectal pathology in children with portal hypertension*

Patient no.	Age (years)	Diagnosis	Symptoms	Findings	Treatment	Outcome
1	6	Idiopathic cirrhosis	Bleeding, prolapse	Haemorrhoids	Injection (twice)	Resolved
2	14	Cystic fibrosis	Bleeding, anal pain	Haemorrhoids, anal fissure	Injection (twice)	Resolved
3	4	EHPVO	Bleeding	Haemorrhoids, anorectal varices	Injection (4 times) Banding (twice)	Resolved
4	6	EHPVO	Bleeding	Haemorrhoids, anorectal varices	Injection (once) Banding (once)	Resolved

EHPVO, extrahepatic portal vein obstruction

these children also had external anal varices. Proctoscopy revealed anorectal varices in 21 children (35 per cent) (internal anal canal varices in 20 (33 per cent), rectal varices in 13 (22 per cent)) and haemorrhoidal vascular cushions in 20 (33 per cent). The rectal mucosa was granular with contact bleeding in two children, an appearance that has been termed 'colopathy'[13]. There was considerable overlap between all categories of anorectal pathology.

Children with haemorrhoidal cushions had been treated more often by oesophageal sclerotherapy than those without abnormality (median (range) 6·5 (0–17) *versus* 1 (0–22) sessions, $P = 0{\cdot}001$) and tended to be older (median 9·5 *versus* 5·5 years). No association was found between the presence or severity of anorectal varices and the number of oesophageal sclerotherapy sessions. There was a higher incidence of haemorrhoids and anorectal varices in children with extrahepatic portal vein occlusion than in those with intrahepatic fibrosis (57 *versus* 26 per cent and 64 *versus* 26 per cent respectively).

The grade of external haemorrhoidal plexus in all groups showed a moderate degree of correlation with the severity of internal anorectal findings (haemorrhoids, $r_S = 0{\cdot}49$, $P = 0{\cdot}004$; rectal varices, $r_S = 0{\cdot}59$, $P = 0{\cdot}001$). Visible external anal varices were always accompanied by internal anorectal pathology.

The presence and severity of rectal varices had a weak correlation with levels of both serum bilirubin ($r_S = 0{\cdot}26$, $P = 0{\cdot}03$) and haemoglobin ($r_S = 0{\cdot}24$, $P = 0{\cdot}04$), but there was no relationship between the presence and degree of haemorrhoids and level of either bilirubin ($P = 0{\cdot}38$) or haemoglobin ($P = 0{\cdot}4$).

Four (7 per cent) of the 60 children had received or were receiving treatment for anorectal symptoms during the study period (*Table 2*).

Discussion

Anorectal pathology has not been widely reported as a significant cause of bleeding in children with portal hypertension[14–16]. The present study has shown that about one-third of children with portal hypertension may have haemorrhoidal cushions or anorectal varices; the incidence of rectal bleeding was 7 per cent.

Anorectal varices may be defined as collaterals between the portomesenteric and systemic venous systems[17] and an increased incidence of such varices might therefore be expected in patients with a raised portal pressure. No anatomical communication has been demonstrated between the haemorrhoidal plexus and the portomesenteric venous system[17]. The relationship in adults between portal hypertension and haemorrhoids remains controversial[18–20] because of the relatively high incidence of the latter in the normal population. Bernstein[18] and Jacobs *et al.*[19] reported haemorrhoids in 28 per cent of adults with cirrhosis, but this figure differs little from that in normal control populations. Hosking *et al.*[3] noted a 63 per cent incidence of haemorrhoids in a prospective series of 100 consecutive patients with cirrhosis undergoing endoscopy for oesophageal varices, but reported no difference in incidence compared with normal controls. Rabinowitz *et al.*[20] found haemorrhoids in only 25 per cent of 412 patients with cirrhosis admitted for transplant assessment. The authors suggested that this was a significant increase in incidence and that the severity of the haemorrhoids, but not rectal varices, was related to the magnitude of portal pressure. The incidence of haemorrhoids in patients with portal hypertension has ranged from 44 to 78 per cent in more recent reports[3,4].

Vascular cushions and venous dilatation are found in the anorectal submucosa of normal children[17], but haemorrhoids do not normally develop at this age[21]. Children with portal hypertension therefore form an ideal group for study and the incidence of haemorrhoids and anorectal varices of 33–35 per cent recorded in the present series provides good evidence for the aetiological role of raised portomesenteric pressure.

Recent prospective studies have revealed anorectal varices in 44–78 per cent of patients with cirrhosis[3,4]. The reported incidence of symptomatic anorectal varices is low, ranging from 0·5 to 5·6 per cent[5,6,8]. The present study has also shown that anorectal venous dilatation in children with portal hypertension can be predicted from the presence of an external anal haemorrhoidal plexus. One-third of the children were found to have anorectal varices and in four (7 per cent) there was significant bleeding. Although direct suture has been required to control bleeding in some patients[8,18], the children in the present study were treated successfully by injection sclerotherapy or banding.

No association between anorectal symptoms and previous endoscopic obliteration of oesophageal varices was demonstrated.

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Surgical workshop

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Intraoperative testing of the Valtrac biofragmentable anastomotic ring

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The biofragmentable anastomotic ring (Valtrac; Davis and Geck, Wayne, New Jersey, USA) is a device used to construct an inverting intestinal anastomosis. It is composed of polyglycolic acid and barium sulphate, and provides a mechanically locking connection that maintains the serosal surfaces of the bowel ends in apposition until healing occurs[1]. Once the two caps of the ring are inserted into the ends of the bowel and the purse-string sutures are tied snugly around the device, the ring is locked by pressing on its caps until they are approximated and 'click' together. However, the instruction manual for the Valtrac ring points out[2]:

> '... click may occur infrequently in the absence of secure closure. Secure closure may occur in the absence of a click. Inspection and gentle traction are recommended to reassure the surgeon that proper closure has been obtained.'

A simple method of testing the closure of the ring without risking disruption of the anastomosis has been devised.

Surgical technique

The ring is grasped with the index and middle fingers and the thumb at the junction between the two caps and gentle pressure applied tangentially (*Figure 1*). If closure is not secure, the two caps separate easily and another attempt can be made to close them. This test has been used in the past 20 colonic anastomoses performed with the ring. In five cases when a click did not occur the test showed the closure to be secure in three, while in the other two the caps separated. In 15 cases where a click did occur, the caps parted during the test in one. In all cases of faulty closure, reapproximation of the caps was successful on a second attempt. No clinical leaks occurred.

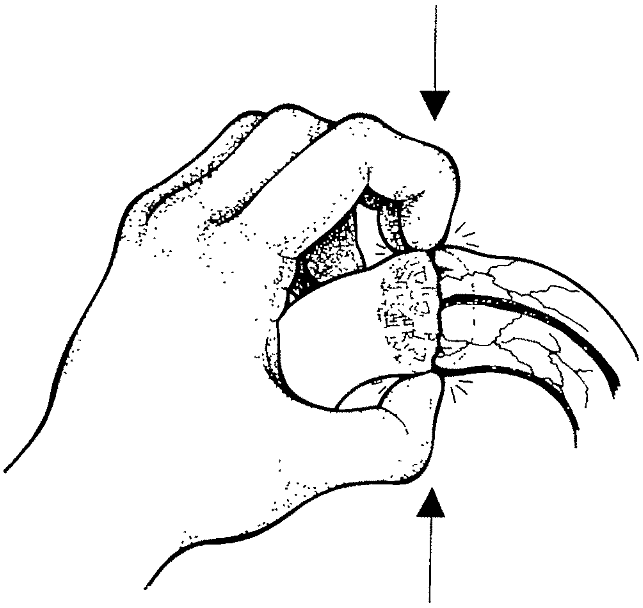

Figure 1 *Intraoperative testing of the biofragmentable anastomotic ring. Arrows indicate points at which gentle pressure was applied to test closure*

Acknowledgements

The authors thank Professor Tiziana Corbani for drawing *Figure 1*.

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Perineural invasion of carcinoma of the pancreas and biliary tract

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Carcinoma of the pancreatobiliary system often produces perineural invasion extending to extrabiliary and extrapancreatic sites. A surgical technique has been developed to manage this invasion and has been used since 1974. Serial sections were prepared from 90 resected specimens and examined for perineural involvement of intramural and extramural biliary plexuses as well as the pancreatic nerve plexus. Perineural invasion was seen in 34 of 40 patients with carcinoma of the common bile duct, in ten of 14 with cancer of the gallbladder and in four of 15 with carcinoma of the papilla of Vater. Invasion extended to the extramural biliary or pancreatic nerve plexuses in 24 of 40 patients with carcinoma of the bile duct. Involvement of the intrapancreatic nerves was seen in all 21 patients with carcinoma of the pancreatic head and that of the pancreatic nerve plexus in 17 of 21. Perineural invasion was often found at the most progressive margin of the tumour. The survival rate of patients with perineural invasion was low compared with that of those without such invasion, although survival of patients with perineural invasion tended to be longer after extensive resection. The perineural space should be regarded as an important route for the spread of pancreatic and biliary carcinoma.

Carcinoma of abdominal organs may spread by local invasion, lymphatic or haematogenous metastasis, and peritoneal dissemination. Local invasion and lymphatic metastasis are of primary concern in the surgical treatment of pancreatic and biliary carcinoma. Perineural involvement has frequently been found to lead to failure of curative resection on histological assessment in patients with pancreatic and biliary carcinoma and to be associated with early postoperative recurrence. Accordingly, a revised surgical procedure[1,2] has been used for the management of such perineural invasion since 1974.

The presence and extent of perineural invasion were studied in patients with pancreatic or biliary carcinoma in an attempt to decrease the number of histologically non-curative operations due to local extension.

Patients and methods

Sixty-nine patients with cancer of the biliary tract and 21 with cancer of the pancreas seen in the authors' department since 1974 were studied. All patients underwent extensive surgery including dissection of regional nerve plexuses and lymph nodes. The surgical procedure involved: (1) retroperitoneal dissection; (2) complete dissection of the nerve plexus in the pancreatic head and superior mesenteric nerve plexus; (3) complete dissection of the hepatoduodenal ligament; (4) resection of the portal vein; (5) total or subtotal pancreatectomy (including duodenectomy) for pancreatic cancer; and (6) right hepatectomy, left hepatic lobectomy, or hilar hepatectomy for carcinoma of the biliary tract.

Excised specimens of tissue with tumour involvement were immediately fixed in 10 per cent buffered formalin. The specimens were then dissected into blocks of about $6 \times 4 \times 0{\cdot}4$ cm. Sections 5 μm thick were cut on a special microtome and stained with haematoxylin and eosin and elastic van Gieson stains. Serial sections of the resected specimens were examined to detect perineural invasion involving the extramural and intramural biliary plexuses or the pancreatic nerve plexus in patients with carcinoma of the biliary tract, and to detect invasion of the pancreatic nerve plexus in those with cancer of the head of the pancreas (*Figures 1* and *2*).

Tumour stage was assessed according to the classification of the Japanese Society of Biliary Surgery[3] and the Japan Pancreas Society[4].

Survival rates were calculated by the Kaplan–Meier method. Outcome was compared using the generalized Wilcoxon test.

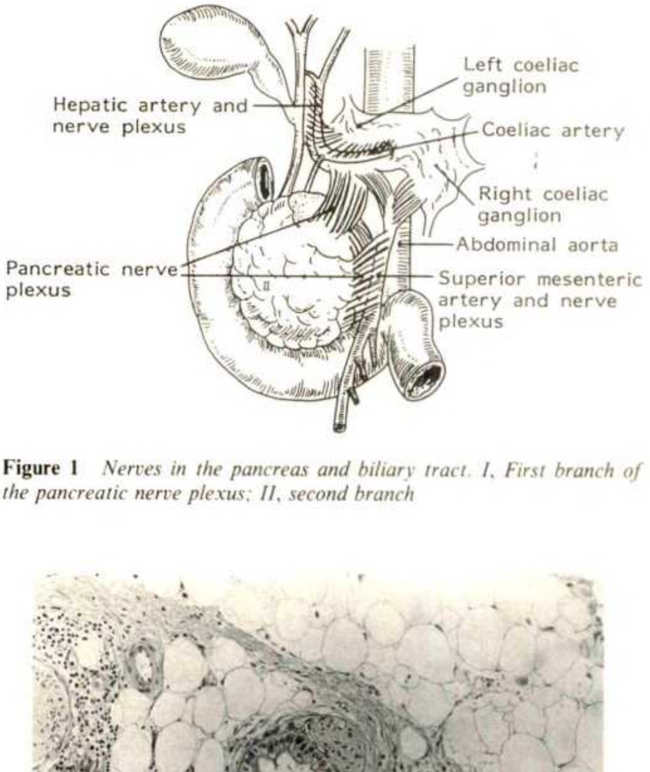

Figure 1 *Nerves in the pancreas and biliary tract. I, First branch of the pancreatic nerve plexus; II, second branch*

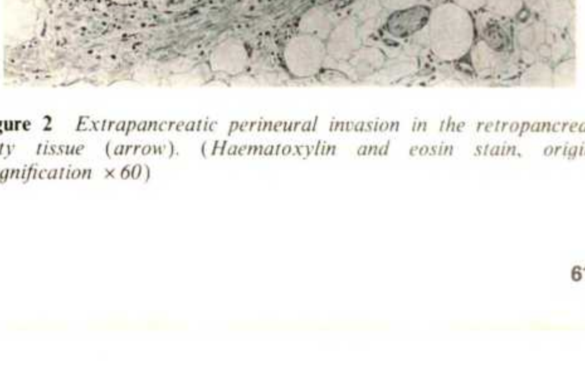

Figure 2 *Extrapancreatic perineural invasion in the retropancreatic fatty tissue (arrow). (Haematoxylin and eosin stain, original magnification ×60)*

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Results

Perineural invasion in carcinoma of the biliary tract

Perineural invasion occurred in 34 of 40 patients with carcinoma of the bile duct, in ten of 14 with cancer of the gallbladder and in four of 15 with carcinoma of the papilla of Vater (*Table 1*).

Invasion was observed in all six patients with carcinoma of the hilar or upper bile duct, and invasion of the extramural plexus was found in four. Of 15 patients with carcinoma involving the middle portion of the bile duct, 14 had involvement of intramural nerves, seven had involved extramural nerves and two had perineural involvement of the pancreatic nerve plexus. In the 19 patients with cancer of the lower bile duct, perineural invasion involving intramural, extramural and pancreatic nerve plexuses was seen in 14, 13 and eight cases, respectively, a notably high proportion even in the pancreatic nerve plexus (*Table 1*).

Perineural invasion was also evaluated according to the stage of cancer (*Table 2*). In carcinoma of the bile duct, patients with stage I cancer had no invasion, but those with stage II, III and IV disease had a high rate of involvement (89 per cent) and extramural invasion in 63 per cent of cases; 38 per cent of patients with stage III and IV cancer had invasion of the pancreatic nerve plexus. In cancer of the gallbladder, patients with stage I and II disease had no perineural invasion, but all those with stage III and IV cancer did. In patients with carcinoma of the papilla of Vater, stage I disease did not include perineural invasion, but 31 per cent of those with stage II, III and IV disease were affected.

Table 1 *Perineural invasion by carcinoma of the biliary tract and pancreas*

	Intramural or intrapancreatic nerves	Extramural nerves	Pancreatic nerve plexus
Carcinoma of the bile duct			
Right and left hepatic ducts and upper bile duct ($n = 6$)	6	4	0
Mid common bile duct ($n = 15$)	14	7	2
Lower common bile duct ($n = 19$)	14	13	8
Total ($n = 40$)	34 (85)	24 (60)	10 (25)
Carcinoma of the gallbladder ($n = 14$)	10 (71)	—	0
Carcinoma of the papilla of Vater ($n = 15$)	4 (27)	—	0
Carcinoma of the head of the pancreas ($n = 21$)	21 (100)	—	17 (81)

Values in parentheses are percentages

Table 2 *Numbers of patients with perineural invasion according to the stage of carcinoma of the biliary tract and pancreas*

	Carcinoma of the bile duct				Carcinoma of the gallbladder		Carcinoma of the papilla of Vater		Carcinoma of the head of the pancreas	
Stage	Absent	Intramural nerves*	Extramural nerves†	Pancreatic nerve plexus‡	Absent	Present	Absent	Present	Intrapancreatic nerves§	Pancreatic nerve plexus #
I	2	0	0	0	3	0	2	0	0	0
II	2	6	4	0	1	0	6	1	1	1
III	2	4	6	4	0	4	3	2	3	12
IV	0	0	4	6	0	6	0	1	0	4

*Intramural invasion only; †includes patients with intramural invasion; ‡includes intramural and extramural invasion; §intrapancreatic invasion only; # includes intrapancreatic invasion

Table 3 *Survival of patients with carcinoma of the biliary tract and pancreas according to extent of neural invasion*

	No. of patients	No. of patients surviving		
		>1 year	>3 years	>5 years
Carcinoma of the common bile duct				
Extramural or pancreatic nerve plexus invasion				
Absent	16	12 (75)	8 (50)	6 (38)
Present	24	14 (58)	9 (38)	5 (21)
Carcinoma of the gallbladder				
Perineural invasion				
Absent	4	4 (100)	4 (100)*	3 (75)
Present	10	4 (40)	2 (20)	2 (20)
Carcinoma of the papilla of Vater				
Perineural invasion				
Absent	11	11 (100)	10 (91)	8 (73)
Present	4	3 (75)	2 (50)	1 (25)
Carcinoma of the head of the pancreas				
Pancreatic nerve plexus invasion				
Absent	4	3 (75)	2 (50)	2 (50)
Present	17	10 (59)	4 (24)	3 (18)

Values in parentheses are percentages. *$P < 0·05$ (perineural invasion absent *versus* present, generalized Wilcoxon test)

Perineural invasion in carcinoma of the head of the pancreas

All 21 patients with carcinoma of the pancreatic head had intrapancreatic perineural involvement and 17 had perineural invasion of the pancreatic nerve plexus (*Table 1*).

Invasion of the pancreatic nerve plexus was observed in one of two patients with stage II disease, 12 of 15 with stage III cancer and all four patients with stage IV disease (*Table 2*).

Survival rates of patients with perineural invasion (Table 3)

Survival rates in patients with cancer at the different sites were compared according to the presence or absence of perineural invasion. That in patients with perineural invasion was lower than that in patients without, but a significant difference in survival rates between the two groups was seen only after >3 years in patients with cancer of the gallbladder.

Discussion

Perineural invasion associated with carcinoma of the biliary tract or pancreas has been well described[3,4]. However, the incidence and clinical significance of perineural involvement extending to extrabiliary, extrapancreatic or pancreatic nerve plexuses have not been fully examined. This phenomenon has been described previously[2,5–7].

Surgical treatment of carcinoma of the pancreatobiliary system achieves unsatisfactory results in comparison with that for cancer of other digestive organs. One factor is the late stage at which many patients present, but the presence of residual cancer cells at the resection margin is also important. According to the present study, 20–40 per cent of cases of apparently resectable carcinoma of the biliary tract and pancreas were histologically non-curative, as tumour cells, particularly those involved in perineural invasion, were observed at the resection margin.

Based on various investigations aimed at improving surgical results, extended dissection of the tumour and lymph nodes has been chosen as the primary surgical procedure for pancreatic and biliary cancer in the authors' department. Examination of the spread of tumour cells by various modes revealed a high incidence of perineural invasion regardless of the size of the tumour or the histological type of the primary lesion, and also demonstrated frequent involvement of the extrabiliary or extrapancreatic plexuses even in patients with small tumours. Extended surgery for pancreatic and biliary carcinoma has been performed in this department since 1974, and in many cases histologically curative resection has been achieved. Before 1974 only two of 12 resections were considered curative, but after that time 27 of 49 thought to be curative on macroscopic appearance were confirmed histologically[2]. The surgical results after 1974 improved significantly compared with those before 1973, with 5-year survival rates for carcinoma of the bile duct and gallbladder increasing from 15 to 37 per cent and from 10 to 30 per cent respectively[6,7]. None of 12 patients with pancreatic cancer operated on before 1974 survived for 5 years; after this time eight of 45 survived for 5 years (an actuarial 5-year survival rate of 31 per cent)[2,8].

The prognosis of patients with perineural invasion is generally poor. In the present study, four patients with perineural invasion were among 11 who survived >3 years after extended surgery. The present results suggest that extended surgery including dissection of the nerve plexuses around the bile duct and behind the pancreas might help to prolong survival.

The reason why pancreatic or biliary carcinoma should frequently invade the perineural tissues is an interesting problem. The perineural space used to be referred to as 'perineural lymphatic', based on the supposed communication of the space with the lymph system, although this is now known not to occur. Perineural invasion is not specific to cancer of the pancreas and biliary tract: it has also been reported in cancer of the prostate and salivary glands as well as in soft tissue sarcoma[9–12]. The high incidence of perineural invasion by pancreatic and biliary carcinoma deserves special attention because the incidence is much lower in cancer of other digestive organs. The rich autonomic innervation of the pancreas and biliary tract may explain this difference. In the authors' experience, perineural lesions are often found in the most advanced portion of the carcinoma. However, the mechanisms of entry of cancer cells into the nerves and the process of proximal invasion along the autonomic plexuses surrounding the pancreas and biliary tract have not been clarified. The possible organ specificity of perineural invasion is another area to be investigated in future studies. The perineural space should be recognized as a potential route for the spread of cancer, with its invasion posing a major problem in surgical treatment.

Lymph node metastasis is another factor that determines prognosis in resection of carcinoma. Long-term survival in patients with metastasis to the lymph nodes around the superior mesenteric artery or to the para-aortic lymph nodes is particularly rare in cancer of the pancreas and biliary tract.

Extended surgery has been performed in the authors' department to cope with the problems of perineural invasion and lymph node metastasis, but the effectiveness of the procedure must be determined by evaluation of a larger number of patients.

Recently, cell adhesion molecules have been described in relation to tumour progression and cancer metastasis[13–15]. Much work remains to be done to determine whether these molecules play a part in perineural invasion in carcinoma of the pancreas and biliary tract.

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Cancer of the gallbladder associated with anomalous junction of the pancreatobiliary duct system without bile duct dilatation

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The aim of this study was to delineate clinical features and prognosis of cancer of the gallbladder associated with anomalous junction of the pancreatobiliary duct system without bile duct dilatation, and to determine methods for managing the disease. A retrospective study of seven patients is presented. A further 27 cases from the Japanese literature were reviewed retrospectively with regard to method of treatment and prognosis. In 11 of 18 patients in whom staging was known the tumour was stage V, representing advanced disease. In seven of 34 cases curative operation was performed; only two patients survived for >3 years. This poor outcome was due largely to delayed diagnosis of cancer of the gallbladder. Prophylactic cholecystectomy is recommended in patients with this anomalous junction without bile duct dilatation or a malignant lesion in the gallbladder, because of the high incidence of cancer of the biliary tract.

Anomalous junction of the pancreatobiliary duct system is a congenital defect defined as the union of the pancreatic and biliary ducts located outside the duodenal wall. Pancreatic juice refluxes into the common bile duct (CBD), or bile juice regurgitates into the pancreatic duct, because the action of the sphincter muscle does not affect the union functionally. Accordingly, there may be various complications such as cholangitis, gallstones, biliary cancer, pancreatitis and pancreatolithiasis[1].

Attention has recently focused on the high incidence of cancer of the biliary tract in this anomaly[2–5]. The incidence of malignant change has been reported as 15–40 per cent[3,4,6,7]. There is an especially high incidence of cancer of the gallbladder in anomalous junction without bile duct dilatation.

The purpose of this study was to delineate clinical features and prognosis of cancer of the gallbladder accompanying this anomaly, and to determine a management strategy for the disease.

Patients and methods

During the 15 years between January 1977 and December 1991, 32 adults with anomalous junction of the pancreatobiliary duct system have been treated in this department. Of these patients, 24 had cystic, fusiform or cylindrical dilatation of the CBD and the other eight no dilatation. Three of the 24 patients and seven of the eight had biliary tract cancer (eight gallbladder, two bile duct). Seven patients with gallbladder cancer without bile duct dilatation are reviewed retrospectively.

The diagnosis of anomalous junction was based on the presence of a long common channel and the anomalous form of junction, according to published criteria[1]. The mean age was 60·7 (range 43–77) years; there were two men and five women. The tumour was staged according to the criteria of Nevin *et al.*[8]: stage I, intramucosal only; II, involvement of mucosa and muscularis; III, involvement of all three layers; IV, involvement of all three layers and the cystic lymph nodes; and V, involvement of the liver by direct extension or metastasis, or metastasis to any other organ.

Results

Clinicopathological features are summarized in *Tables 1* and *2*. The majority of patients were first seen with abdominal pain. Cervical lymph node swelling was noted in one. One patient (no. 5) was free from symptoms related to the disease; a mass in the gallbladder was discovered at ultrasonography for abdominal aneurysm. Serum carcinoembryonic antigen levels were abnormally high in two cases. The diagnosis of cancer of the gallbladder was made before operation in all patients. Maljunction was detected by preoperative endoscopic retrograde cholangiopancreatography in four patients and by intraoperative cholangiography in three.

The mean length of the common channel was 26·7 (range 20–35) mm. The mode of junction in six cases was with the pancreatic duct entering the bile duct; in one case the bile duct entered the pancreatic duct. Two cholangiopancreatograms representative of the anomaly are shown in *Figure 1*. The amylase level in the bile, determined in four patients, was very high. There were no gallstones in any case. In only two patients was the tumour limited to the gallbladder wall (stage III).

Surgical resection was possible in the two patients with stage III disease, and in the three with stage IV tumours (*Table 2*). In the two patients with stage V disease, only laparotomy and tumour biopsy were performed because of massive invasion of the liver and distant metastasis.

In three patients (nos 1, 2 and 3) the resection performed was considered non-curative because of tumour involvement at the resection margin. Curative resection was performed in only two cases. Lymph node involvement was present in five patients; histological diagnosis is shown in *Table 2*. There was no operative death. One patient who underwent curative operation is still alive after 38 months. The other six patients died from progression of the tumour within 3–30 months.

Review of the Japanese literature

A total of 34 cases were reviewed: the present seven and a further 27 from the Japanese literature[2,9–11], of cancer of the gallbladder accompanied by the anomaly without bile duct dilatation, for which the method of treatment and prognosis had been described adequately. In 18 cases tumour stage had been determined using the criteria of Nevin *et al.*[8]. Only two patients had stage III disease; the other 16 had stage IV or V tumours.

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Table 1 *Clinical features in patients with cancer of the gallbladder associated with pancreatobiliary maljunction without bile duct dilatation*

Patient no.	Age (years)	Sex	Chief complaint	CEA concentration (ng/ml)	Length of common channel (mm)	Mode of junction	Amylase concentration in bile (units)	Gallstones
1	43	F	Abdominal pain	1·0	26	P–B	—	None
2	72	F	Abdominal pain	2·9	20	P–B	109 520	None
3	55	F	Abdominal pain	0·9	30	P–B	139 490	None
4	53	M	Abdominal pain	65·1	35	B–P	147 170	None
5	77	M	None	1·9	23	P–B	302 790	None
6	63	F	Cervical lymph node swelling	2·1	28	P–B	—	None
7	58	F	Abdominal pain	13·8	25	P–B	—	None

CEA, carcinoembryonic antigen (normal range <5 ng/ml); P–B, pancreatic duct entering bile duct; B–P, bile duct entering pancreatic duct

Table 2 *Clinicopathological findings in patients with cancer of the gallbladder associated with pancreatobiliary maljunction without bile duct dilatation*

Patient no.	Tumour			Operation	Curative	Differentiation of adenocarcinoma	Depth of tumour invasion	Lymph node metastasis	Outcome
	Size (mm)	Location	Stage*						
1	60 × 67	Neck and body	III	Cholecystectomy, lymphadenectomy	No	Poor	Serosa	No	Died at 11 months
2	40 × 60	Neck, body and fundus	IV	Cholecystectomy, lymphadenectomy	No	Moderately differentiated tubular	Subserosa	Yes	Died at 12 months
3	50 × 60	Neck, body and fundus	IV	Pancreatoduodenectomy, hepatic subsegmentectomy, lymphadenectomy	No	Well differentiated tubular	Serosa	Yes	Died at 11 months
4	30 × 44	Body	IV	Pancreatoduodenectomy, hepatic subsegmentectomy, lymphadenectomy	Yes	Papillary	Serosa	Yes	Died at 30 months
5	25 × 10	Neck and body	III	Cholecystectomy, lymphadenectomy, hepatic wedge resection	Yes	Moderately differentiated tubular	Subserosa	No	Alive at 38 months
6	—	Neck, body and fundus	V	Exploratory laparotomy	—	Well differentiated tubular	Other organs	Yes	Died at 3 months
7	—	Neck, body and fundus	V	Exploratory laparotomy	—	Poor	Other organs	Yes	Died at 6 months

*According to Nevin *et al.*[8]

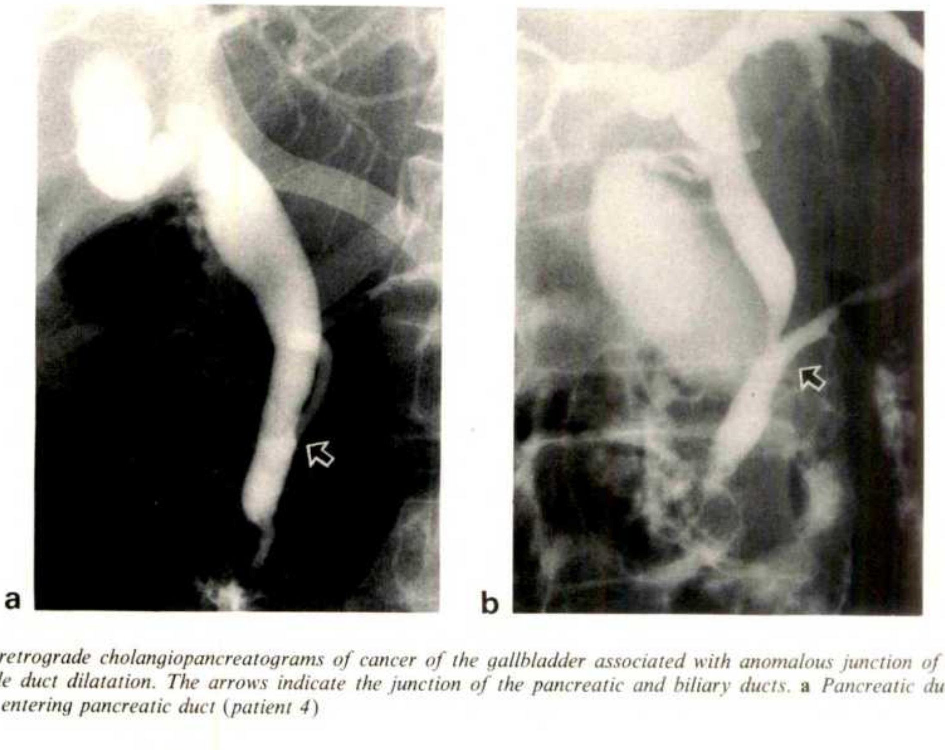

Figure 1 *Endoscopic retrograde cholangiopancreatograms of cancer of the gallbladder associated with anomalous junction of the pancreatobiliary duct system without bile duct dilatation. The arrows indicate the junction of the pancreatic and biliary ducts.* **a** *Pancreatic duct entering bile duct (patient 3);* **b** *bile duct entering pancreatic duct (patient 4)*

The following operations had been performed: curative cholecystectomy with or without hepatic resection (six cases); palliative cholecystectomy (nine); pancreatoduodenectomy (three); right hepatic lobectomy (one); external biliary drainage (seven); bilioenteric anastomosis (two); exploratory laparotomy (four); and no operation (two).

Curative operation was performed in seven cases. Only two patients survived for >3 years after surgery; 24 died within 1 year.

Discussion

Aoki *et al.*[4] analysed 569 patients in Japan with anomalous junction of the pancreatobiliary duct system. Dilatation of the extrahepatic bile duct was found in most of the patients (cystic 44 per cent, spindle 23 per cent, cylindrical 17 per cent); no dilatation was present in only 80 cases (14 per cent). A total of 131 patients (23 per cent) had associated cancer of the biliary tract; 93 had carcinoma of the gallbladder, 31 cancer of the bile duct, and seven cancer of unknown location.

There were some characteristic clinical features. In patients <30 years of age, a bile duct of normal calibre was found in only 2–5 per cent, but the incidence increased gradually in those aged ≥ 30 years, reaching 31 per cent[4] for patients aged 60–69 years. Of 253 patients with cystic dilatation only 30 (12 per cent) had associated cancer of the biliary tract (gallbladder, nine; bile duct, 21), but of 80 patients with no dilatation, 49 (61 per cent) had this cancer (gallbladder, 44; bile duct, four; and unknown location, one). This high incidence of malignancy might be explained by reflux of pancreatic juice into the gallbladder with consequent chronic cholecystitis with intestinal metaplasia, a precancerous condition leading to differentiated carcinoma[2]. The mechanism of concentration of bile in the gallbladder may also promote cancerous change[4,12].

A total of 34 patients with cancer of the gallbladder associated with anomalous junction without bile duct dilatation, including 27 previously reported and the present seven, are reviewed in this paper. In the majority of patients in whom staging was known (11 of 18), the tumour was stage V, representing advanced disease. In seven of 34 patients curative operation was performed, but only two survived for >3 years after operation. This dismal outcome is due largely to delayed diagnosis of cancer of the gallbladder. The incidence of gallstones in patients with this cancer associated with anomalous junction is very low[4,5] compared with that in those with cancer of the gallbladder not accompanied by anomalous junction[13–15]. The low incidence of gallstones may make the early diagnosis of cancer of the gallbladder difficult, because the tumour will have become widespread by the time symptoms associated with the cancer occur. Cure following cholecystectomy is possible when the malignant lesion is limited to the mucosa or muscularis propria[8,15,16]. Early diagnosis is therefore essential for the successful treatment of cancer of the gallbladder.

For patients with anomalous junction without bile duct dilatation in whom there is no malignant lesion in the gallbladder, prophylactic cholecystectomy is recommended because of the high incidence of cancer of the biliary tract.

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Management of non-functioning neuroendocrine tumours of the pancreas

Between 1982 and 1991, 20 patients of median age 44 (range 22–76) years were treated for non-functioning neuroendocrine tumours of the pancreas. Presenting features were obstructive jaundice (seven patients), abdominal pain (seven), weight loss (six), abdominal mass (eight) and severe haemorrhage (four). Gut hormone profiles were normal except for one patient who had a raised pancreatic polypeptide level. Contrast-enhanced computed tomography localized the tumour in 17 patients and visceral angiography in 14 of 15; all but three tumours were highly vascular. Ten patients underwent curative resection, and the remainder were managed palliatively by resection (four), bypass procedures (three) or biopsy alone (three). There were two postoperative deaths and seven early complications. Seven of the remaining 18 patients have died from disease a median of 16 (range 4–30) months after presentation. The 11 survivors, eight of whom had curative resections, have been followed for a median of 42 (range 7–72) months. Ten patients are asymptomatic but only five are free from disease. These tumours are seldom curable by radical surgery, but patients may remain free from symptoms for many years.

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Pancreatic neuroendocrine (islet cell) tumours are rare, occurring in <1 per 100 000 population[1]. Most present with features of a specific clinical syndrome caused by excess production of a single hormone. Some tumours produce more than one hormone which may result in a combination of clinical syndromes or transition from one to another. Between 15 and 41 per cent of tumours seem to be non-functioning: they are not associated with a clinical syndrome and do not produce an excess of any active peptide[2–4]. Malignant neuroendocrine tumours are more commonly non-functioning (44–67 per cent[5–8]); these lesions tend to present later and have a different clinical course from their functioning counterparts.

Clinical presentation, diagnosis, management and outcome in 20 patients with non-functioning neuroendocrine tumours of the pancreas have been reviewed to determine the natural history and optimum management of such lesions.

Patients and methods

A total of 20 patients with non-functioning neuroendocrine tumours were treated between 1982 and 1991. Seventeen had been investigated elsewhere and some had undergone exploratory laparotomy before referral. Measurement of levels of circulating plasma peptides (gastrin, glucagon, neurotensin, pancreatic polypeptide, vasoactive intestinal peptide (VIP)) was carried out in all patients. Concentrations of other peptides such as insulin, somatostatin and 'ectopic' hormones were selectively measured. Radiological investigations included computed tomography (CT), selective visceral angiography, ultrasonography, barium meal, endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC). The diagnosis of a neuroendocrine tumour was made by histological and immunohistochemical examination. Evidence of malignancy was determined by peripancreatic extension of the tumour, lymph node involvement or metastasis to extrapancreatic sites. The tumour was resected where possible, as a curative or palliative procedure. Resection in the presence of liver metastases was regarded as palliative even if the metastases were completely excised.

Outcome was determined by assessing symptoms, monitoring plasma hormone levels (nine patients), further radiological scanning (15) and from the length of survival. Length of survival from initial presentation and from definitive treatment are given separately, as a delay in diagnosis and management was not uncommon.

Results

The 20 patients (ten men, ten women) had a median age of 44 (range 22–76) years.

Clinical presentation

The main presenting features were obstructive jaundice (seven patients), pain (seven), weight loss (six), a palpable abdominal mass (eight), gastrointestinal bleeding (two) and intra-abdominal haemorrhage (two). Associated symptoms included anorexia, nausea, vomiting and diarrhoea. None of the patients displayed the clinical features of an endocrine disorder. Gastrointestinal bleeding was caused by tumour eroding into the posterior wall of the stomach (one patient) or medial wall of the duodenum (one). Two patients developed spontaneous retroperitoneal bleeding from the tumour and presented with hypovolaemic shock and an abdominal mass.

The median duration from onset of symptoms to diagnosis was 3 (range 0·5–108) months. Tumour was almost certainly the cause of recurrent attacks of acute pancreatitis in two patients with 4- and 9-year histories; one of these patients with jaundice underwent laparotomy at which no tumour was palpable. When reassessed 2 years later, the patient had a pancreatic neuroendocrine tumour with a solitary liver metastasis. A patient whose father died from a VIPoma had been treated for hyperparathyroidism and papillary carcinoma of the thyroid. An abnormality of the pancreas was noted on CT 2 years before referral with symptoms of weight loss and steatorrhoea.

Investigations

Hormone profiles. Plasma hormone levels were normal in 19 of the patients. One had a pancreatic polypeptide level >1000 pmol/l (normal <300 pmol/l).

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Imaging. Preoperative diagnosis and localization were determined by CT (20 patients) and angiography (15). ERCP (seven patients) or PTC (nine) was performed to determine the cause of obstructive jaundice; a barium meal was obtained in six patients with suspected duodenal obstruction. Tumours were successfully localized by CT in 17 patients. No pancreatic lesion was seen in three patients: in two the lesions were seen on angiography and the third was found at operation. Angiography showed a mass lesion in the region of the pancreas in 14 of 15 patients; 11 of these were highly vascular and three relatively avascular.

Metastatic liver lesions were present in five patients and were shown by CT and angiography (two), CT alone (one) or angiography alone (two). In one patient angiography showed a pancreatic lesion of limited vascularity associated with two highly vascular lesions in the liver (*Figure 1*). At operation, there was a neuroendocrine tumour diffusely involving the pancreas, but the liver lesions were benign (hepatic adenoma and focal nodular hyperplasia).

Biopsy. Histological diagnosis was obtained before operation in five patients: by guided biopsy under ultrasonographic or CT control (three), endoscopic biopsy (one) and cervical lymph node biopsy (one). Operative biopsy was performed at laparotomy in six patients before referral; three of these had required emergency operations to try to stop bleeding.

Treatment

Fourteen patients underwent resection of the pancreatic tumour (*Table 1*). Four of these procedures were palliative resections in the presence of liver metastases; local excision of a solitary metastasis was carried out in two patients and debulking of multiple metastases in a third. Three patients had a bypass. No definitive procedure was performed in another three: two were found to have irresectable tumours at laparotomy and the third had tumour spread to the cervical lymph nodes.

There were two postoperative deaths, at 26 and 39 days. One patient died from progression of cancer after a palliative bypass and the other from rupture of a false aneurysm of the superior mesenteric artery after curative resection of a tumour that had caused recurrent retroperitoneal haemorrhage. There were seven early complications in the remaining patients: transient pancreatic fistula, transient faecal fistula, bleeding from a liver metastasis biopsy site (controlled by therapeutic embolization), superior mesenteric vein thrombosis and adhesion obstruction (each requiring reoperation), intra-abdominal abscess, and chest infection. One patient subsequently developed a postgastrectomy syndrome following Whipple's procedure.

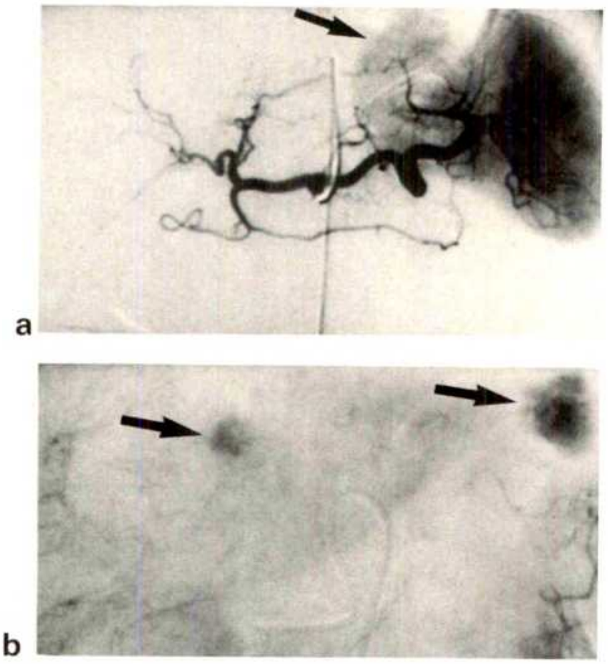

Figure 1 *Coeliac angiography in a 36-year-old woman with a large neuroendocrine tumour arising in the body of the pancreas but extending throughout the gland.* **a** *The splenic arteriogram shows limited vascularity in the region of the distal pancreas (arrow).* **b** *The late-phase hepatic arteriogram shows two discrete tumours (arrows) in the left liver that blushed intensely and were erroneously thought to represent metastases. The two hepatic lesions were excised during total pancreatectomy; one was a benign adenoma and the other an area of focal nodular hyperplasia*

Table 1 *Details of operations performed on 20 patients with non-functioning neuroendocrine tumours*

Operation	Curative ($n = 10$)	Palliative ($n = 10$)
Total pancreatectomy and splenectomy	2	0
Pylorus-preserving pancreatoduodenectomy	3	2*
Whipple's procedure	2‡	0
Distal pancreatectomy plus splenectomy	2	2†
Partial pancreatectomy	1	0
Choledochoenterostomy with or without gastroenterostomy	0	3
Arrest bleeding and biopsy	0	2
Biopsy alone	0	1

*Solitary liver metastasis in both; †multiple liver metastases in both; ‡right hemicolectomy plus superior mesenteric vein excision in one patient

Table 2 *Distribution of 20 neuroendocrine tumours within the pancreas*

Site	No.
Head alone	9
Head and uncinate process	2
Uncinate process alone	1
Neck	2
Body alone	1
Body and tail	2
Tail alone	2
Diffuse	1

Adjuvant radiotherapy was given to one patient after a curative operation because histological examination revealed tumour cells at the resection margin. Four patients undergoing palliative procedures were given radiotherapy or chemotherapy (streptozotocin alone or in combination with 5-fluorouracil).

Pathology

Histopathology. The sites of the tumours are detailed in *Table 2*. The median tumour diameter was 8 (range 0·6–15) cm. Perineural and vascular invasion were noted in several tumours and two contained areas of ossification, which had been noted on CT. Of the patients undergoing curative resection, five had lymph node metastases and four had peripancreatic tumour extension into the spleen, transverse mesocolon and superior mesenteric vein, stomach or duodenum. In those undergoing palliative treatment, liver metastases were present in five patients; one tumour extended directly into the liver and one patient had lung and cervical lymph node metastases.

Immunohistochemistry. At least one of the general markers for neuroendocrine tumours (neurone-specific enolase, chromogranin or Grimelius stain) was present in all tumours. A total of 11 of 15 tumours showed clear-cut immunoreactivity for specific peptides; three stained for C peptide, one for pancreatic polypeptide, one for somatostatin and the remainder for several different peptides. One patient previously treated for hyperparathyroidism and thyroid carcinoma had two small adjacent pancreatic tumours secreting different peptides as well as a carcinoid tumour in the appendix. One tumour showed immunoreactivity for VIP and pancreatic polypeptide, and the other for glucagon-like peptide 1, insulin and somatostatin.

Outcome

Apart from the two postoperative deaths, seven of the remaining 18 patients died at a median of 16 (range 4–30) months from initial presentation. Eleven patients are alive at a median of 42 (range 7–72) months. The overall median survival from presentation was 30 (range 4–72) months.

Curative resection. The median survival of the nine patients who underwent curative resection and left hospital alive was 42 (range 4–72) months from presentation and 36 (range 4–72) months from operative resection. Eight patients are alive, and one died from liver metastases 4 months after resection of an extensive tumour involving the portal vein. Five patients are disease-free with a median survival of 30 (range 12–36) months, including one who underwent subsequent resection of the liver. Plasma hormone levels have remained normal.

Palliative treatment. The median survival from presentation of patients managed palliatively was 32 (range 13–63) months and from the palliative operation 16 (range 4–63) months. Only three patients are still alive.

Discussion

Non-functioning neuroendocrine tumours are identical developmentally and histologically to functioning tumours but differ in their clinical course and outcome. Lacking the features of an endocrine syndrome, they seldom present until there is advanced local disease or distant metastasis[3,9,10]. Delay in diagnosis is common: mean delays of 5 months to 2–7 years have been reported[2,3,11]. The presenting features are those of a pancreatic mass and include jaundice, pain, weight loss and a palpable lump. Life-threatening haemorrhage caused by direct infiltration of blood vessels by tumour is a rare presentation but was found in four of the present patients, two of whom have been previously reported[12]. Another potential cause of bleeding is from gastric varices produced by left-sided portal hypertension in association with splenic vein thrombosis[13].

The investigations of choice to localize these tumours are contrast-enhanced CT and selective visceral angiography. Radiological features characterizing non-functioning neuroendocrine tumours as opposed to pancreatic adenocarcinoma are unusually large size, calcification within the tumour and vascularity. Eelkema and colleagues[9] found calcification in six of 27 tumours; two of the present 20 patients had calcification (or rather ossification).

Circulating peptide levels are usually normal in non-functioning tumours, but their secretory characteristics may change; in one of the present patients a raised pancreatic polypeptide concentration reverted to normal after 3 years despite progressive disease. Heitz and co-workers[14] performed immunohistochemical studies on 30 non-functioning pancreatic neuroendocrine tumours. Peptide-producing cells were detected in 26 patients, all of whom had normal serum hormone levels, and 15 tumours contained multiple peptides. The present findings are similar. Pancreatic neuroendocrine tumours may be associated with other neuroendocrine tumours. One patient in the present study had two pancreatic tumours secreting different peptides plus hyperparathyroidism and an appendicular carcinoid (multiple endocrine neoplasia syndrome type I). The reported rate of malignancy of non-functioning neuroendocrine tumours is 60–92 per cent[2,3,11]; only two of the present 20 patients appeared to have benign tumours.

Non-functioning neuroendocrine tumours are resectable in 36–100 per cent[5,10,11] of patients, although potentially curative resections are possible in only 27–57 per cent[2,3,6,11]. In the present study, operation was potentially curative in half the patients but several had locally advanced disease (including two with involvement of the superior mesenteric or portal vein). The overall complication rate of 39 per cent (25 per cent after resection) and mortality rate of 10 per cent are high but comparable to findings in other studies[3,6].

Survival rates at 5 years of 35–63 per cent have been reported for patients with non-functioning tumours[2,3,6,10]. Those with functioning lesions have longer survival[3,6] but Venkatesh and colleagues[5], in a series of 98 patients, showed that the poorer prognosis associated with non-functioning tumours seemed to be because such patients presented with more advanced disease. In the present study one of ten patients died after potentially curative resection and the remainder were followed for a median of 36 months with one late death, whereas two-thirds of those managed palliatively died from disease at a median of 16 months after operation. This difference in survival probably reflects the different stage of disease at the time of presentation. Prolonged survival is possible with advanced disease; this makes it difficult to determine the survival benefit of curative resection over palliative treatment.

These tumours cause troublesome symptoms as they increase in size and compress or invade adjacent structures such as the duodenum or bile duct. Resection is probably the best treatment whether curative or palliative, but it should not be undertaken if there is serious risk because these patients may have prolonged survival with non-operative treatment. Adjuvant chemotherapy with streptozotocin relieves symptoms in up to 60 per cent of patients with irresectable neuroendocrine tumours, and better results may be obtained by adding 5-fluorouracil[15,16].

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Temporary loop ileostomy for restorative proctocolectomy

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The aim of a defunctioning ileostomy after restorative proctocolectomy is to mitigate the consequences of pelvic sepsis, should it occur. However, there are complications related to the ileostomy itself. Of 310 patients (174 male and 136 female; mean age 33·2 years) who underwent restorative proctocolectomy between 1976 and 1990, 296 had a covering ileostomy and 14 did not. The stoma has been closed in 263 (88·9 per cent) at a median interval from formation of 12·0 weeks. Ileostomy-related complications before closure occurred in 17 patients (5·7 per cent). Laparotomy for obstruction due to the ileostomy was required in seven patients (2·4 per cent). Retraction requiring revision occurred in three patients (1·0 per cent), an abscess behind the stoma in one (0·3 per cent) and miscellaneous appliance problems in seven (2·4 per cent). Following closure, 59 patients overall (22·4 per cent) developed an ileostomy-related complication. There were 30 cases of small bowel obstruction, treated conservatively in 19 (7·2 per cent) and by laparotomy in 11 (4·2 per cent). Peritonitis requiring laparotomy occurred in three patients (1·1 per cent) and two (0·8 per cent) developed an enterocutaneous fistula. There were 14 (5·3 per cent) wound infections and 16 (6·1 per cent) other miscellaneous problems. Significant complications associated with a temporary ileostomy were less frequent in this series than in some other reports. Obstruction was the most common complication and fistula was rare.

In early descriptions of restorative proctocolectomy[1–3] a protective ileostomy was recommended. However, use of this procedure is associated with a complication rate that may be high[4]. As a result some surgeons have questioned the necessity for an ileostomy. Others, however, have reported a low morbidity rate and continue to advocate use of the procedure[5]. In this paper the complications associated with a temporary ileostomy used routinely in most cases at this hospital are reviewed.

Patients and methods

Between 1976 and 1990, 310 patients underwent restorative proctocolectomy or proctectomy with an ileoanal reservoir, with a covering ileostomy in 296 and without in 14. There were 174 male and 136 female patients; the mean age was 33·2 (range 14–64) years. There were 272 patients with ulcerative colitis, of whom 14 also had carcinoma, and 35 with familial adenomatous polyposis, of whom ten had carcinoma. Three had functional bowel disease including one patient with megacolon. All complications related to the ileostomy both before and after closure were noted as well as those related to healing of the ileoanal anastomosis and the ileal reservoir itself. Other variables analysed included steroid medication at the time of surgery, the seniority of the surgeon who closed the ileostomy, the type of closure, whether lateral or end to end, and the suture material used.

Of the 296 patients with a covering ileostomy, the stoma was closed at this hospital in 263. The stoma had been closed elsewhere in 15 patients and the ileostomy had not been closed in 12; in four the pouch had been excised before closure and two patients had died. There were therefore 296 patients available for assessment before closure and 263 after.

The median interval to closure was 12·0 (range 1·6–101) weeks. In 98 patients (37·3 per cent) the stoma was closed by a consultant and in 165 (62·7 per cent) by a senior registrar.

Results

Before closure

Seventeen patients (5·7 per cent) had 18 complications related to the ileostomy before closure (*Table 1*). Eight complications (2·7 per cent) were minor and ten (3·4 per cent) major. All ten major complications required a laparotomy either for intestinal obstruction (seven cases) or retraction of the stoma (three). Seven patients had the ileostomy excised and closed, and one had it excised and refashioned. No major small bowel resections were performed.

A total of 35 patients (11·8 per cent) developed small bowel obstruction after pouch formation before closure. A laparotomy was performed in 12 patients; in seven (see above) this resulted from obstruction due to the ileostomy. Thus the ileostomy was responsible for small bowel obstruction in more than half of the patients requiring a laparotomy for obstruction before stoma closure.

After closure

In five (1·9 per cent) of the 263 patients the ileostomy had to be closed by exposure gained by a laparotomy. In addition 59 patients (22·4 per cent) had 65 complications after closure of the ileostomy (*Table 2*). Sixteen (6·1 per cent) of these events were major and 49 (18·6 per cent) minor. Thirty patients (11·4 per cent) developed small bowel obstruction attributable to ileostomy closure. Of these, 11 (4·2 per cent) needed a laparotomy. Eighteen other patients required a laparotomy for small bowel obstruction that was not due to the ileostomy. Three patients developed peritonitis after operation, in one resulting from damage to an adjacent loop of bowel, in one from perforation of the ileostomy site 3 months later, and in one no cause could be found. Only two patients (0·8 per cent) developed an enterocutaneous fistula; one (0·4 per cent) required a laparotomy.

Complications of the ileoanal anastomosis with pelvic abscess formation occurred in 47 (15·9 per cent) of the 296 patients having an ileostomy and in two (14 per cent) of the 14 without. Both of these latter patients developed a faecal fistula. Eighty-two patients (26·5 per cent) were taking steroids at the time of pouch formation. There was no significant

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Table 1 *Complications of ileostomy before closure of the stoma in 296 patients*

	No.
Small bowel obstruction due to ileostomy necessitating laparotomy†	7 (2·4)
Retraction needing revision†	3 (1·0)
Abscess behind stoma	1 (0·3)
Appliance problems	7 (2·4)
Total no. of laparotomies	10 (3·4)
Total no. of complications*	18 (6·1)

Values in parentheses are percentages. *In 17 patients (5·7 per cent); †major complications (3·4 per cent)

Table 2 *Complications of ileostomy after closure of the stoma in 263 patients*

	No.
Small bowel obstruction treated conservatively within 2 months	19 (7·2)
Small bowel obstruction due to ileostomy necessitating laparotomy†	11 (4·2)
Peritonitis necessitating laparotomy†	3 (1·1)
Enterocutaneous fistula	
Managed conservatively	1
Necessitating laparotomy	1
Total†	2 (0·8)
Wound infection	14 (5·3)
Miscellaneous	
Prolonged ileus	2
Pain in scar	2
Stitch sinus	2
Chest infection	2
Deep vein thrombosis	2
Wound haematoma	1
Pyrexia	1
Unsightly scar	1
Dehydration	1
Pneumoperitoneum	1
Rectal bleeding	1
Total	16 (6·1)
Total no. of laparotomies	15 (5·7)
Total no. of complications*	65 (24·7)

Values in parentheses are percentages. *In 59 patients (22·4 per cent); †major complications (6·1 per cent)

difference in the development of pelvic sepsis or anastomotic complications between those receiving steroid medication or not (χ^2 = 2·03, 1 d.f., $P > 0{\cdot}1$). However, a significantly higher number of patients taking steroids developed a complication related to the ileostomy (35 *versus* 20 per cent; χ^2 = 6·31, 1 d.f., $P < 0{\cdot}02$).

The incidence of ileostomy-related morbidity was not linked to the type of suture material used or the seniority of the surgeon. In all, 102 patients (39·4 per cent) had the ileostomy closed by resection and end-to-end anastomosis, 157 (60·6 per cent) had it closed by mobilization and primary closure and in four the method was not recorded. There was no relationship between the method of closure and the complication rate; in particular, the incidence of obstruction (10·8 and 12·1 per cent) was similar in both groups.

Further surgery for complications of the ileostomy was needed after closure in a total of 20 patients (7·6 per cent), including five (1·9 per cent) who had a laparotomy to close the stoma. Of these, obstruction was the reason in 11 patients (4·2 per cent). A short segment of small bowel was resected in seven patients at the time of laparotomy. In the whole series of 296 patients, obstruction due to the ileostomy necessitated a laparotomy in 18 (6·1 per cent).

Discussion

In this series the overall complication rate, while significant, was low. In particular the faecal fistula rate of 0·8 per cent compares favourably with that found in other series[5] and especially with the incidence of 18 per cent reported by Winslett *et al.*[4]. On the basis of the present results the risk of faecal fistula formation after closure cannot be regarded as a contraindication to a defunctioning ileostomy.

Small bowel obstruction was the major source of morbidity. The overall incidence after restorative proctocolectomy in the present series of 12·5 per cent is similar to those reported by others[6–9]. Patients requiring a laparotomy (for small bowel obstruction related to the ileostomy) before closure of the stoma at 2·4 per cent were fewer than the 6·4 per cent of another series[10]. After ileostomy closure the overall incidence of small bowel obstruction at 11·4 per cent compares favourably with those found by others[5,8,10]. Obstruction in this series was taken to include events that occurred up to 2 months after surgery, whereas other authors[4] have included events up to 10 days only. This may account for the lower incidence of small bowel obstruction (6 per cent) in their series. The laparotomy rate for obstruction after closure of the stoma (4·2 per cent) is also similar to the experience of others[4,5,8,10]. The problem of small bowel obstruction is not confined to restorative proctocolectomy and is seen in a similar proportion of patients after other operations for ulcerative colitis[11,12]. However, in some patients following restorative proctocolectomy, the obstruction can be ascribed directly to the temporary ileostomy.

Retraction of the ileostomy rarely posed a serious problem. It is likely that some minor problems dealt with by the stoma therapist after operation did not come to the notice of the doctor. Only 1·0 per cent of the present patients needed revision of the stoma compared with 6·4 per cent reported by Metcalf *et al.*[10] and 4·3 per cent by Feinberg and colleagues[8]. The incidence of less severe forms of retraction not requiring surgery has been reported[4] to be as high as 29 per cent.

Closure of the ileostomy necessitated a laparotomy in 1·9 per cent of patients in the present series, which compares favourably with other reports[4]. Pemberton *et al.*[6] found a laparotomy necessary in 17 per cent of patients. This difference is presumably related to the surgeon's preference. From the experience reported in the present study, closure without laparotomy can be carried out safely in almost all cases.

Laparotomy for peritonitis was performed in three patients (1·1 per cent) in the present series, a lower incidence than the 7·4 per cent quoted by Metcalf *et al.*[10]. The reason for this difference is not clear.

Conventionally, protective ileostomy has been part of surgical treatment and, while its presence has probably mitigated the effects of pelvic sepsis, it is not possible to judge from these uncontrolled data whether the incidence of sepsis might have been higher or consequences different without a stoma. Pelvic sepsis is common following restorative proctocolectomy. In the present series the rate (15·9 per cent) was similar to those reported by others[5,9,10,13].

In the small number of patients in the present series in whom no defunctioning ileostomy was carried out, the incidence of pelvic sepsis was not increased. Two of these patients developed a faecal fistula, of whom one required a temporary ileostomy which has been closed with a good functional result. Everett[14] reported a 20 per cent complication rate in a selected group of 20 patients who did not have an ileostomy, but only two subsequently required a temporary stoma. Thow[15] reported on 21 selected patients without an ileostomy; a postoperative stoma was required in only one.

Other authors have noted a significantly higher incidence of pelvic sepsis without a defunctioning ileostomy. Goldberg and Rothenberger[13] reported an incidence of 83 per cent in a small series of six patients not having an ileostomy. Metcalf *et al.*[10] found the incidence of pelvic sepsis to be significantly higher (44 per cent) in patients with an incompletely defunctioning ileostomy compared with 14 per cent after complete diversion. In another small series of selected patients, however, the same authors had a more favourable outcome[16]. Kmiot and Keighley[17] had a complication rate of 19 per cent without the use of an ileostomy.

Ileostomy can be performed with minimal serious morbidity, although there are significant complications. These appeared to be fewer in the present series than reported by others[4,6,10]. There is no way of knowing how beneficial ileostomy has been in the present patients. However, long-term results have been good.

A prospective randomized trial comparing restorative proctocolectomy with and without a defunctioning ileostomy is required. Although a defunctioning ileostomy will always be indicated in some patients for technical reasons (including difficulties in the construction of the ileoanal anastomosis), or when the disease is severe, it seems probable that increasing numbers of pouches will be constructed without an ileostomy.

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Editor's note

Readers are referred to a recently published prospective randomized study of restorative proctocolectomy with and without covering ileostomy:

> Grobler SP, Hosie KB, Keighley MRB. Randomized trial of loop ileostomy in restorative proctocolectomy. *Br J Surg* 1992; **79**: 903–6.

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Possible role of the autonomic nervous system in sphincter impairment after restorative proctocolectomy

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Peroperative manometry was performed in 12 patients operated on with endoanal proctectomy and a hand-sewn pouch–anal anastomosis and in 12 in whom proctectomy was performed entirely from above, with the ileal pouch stapled to the top of the anal canal. Results from both groups showed that division of the superior rectal artery reduced the median (95 per cent confidence interval (c.i.)) resting anal pressure from 77·5 (69·9–83·3) mmHg to 64·5 (55·2–70·0) mmHg ($P < 0{\cdot}01$)*. Complete rectal mobilization to the pelvic floor decreased resting pressure by an additional 22 per cent, to a median of 50·0 (95 per cent c.i. 40·1–53·5) mmHg* ($P < 0{\cdot}01$)*. After completion of anastomosis, irrespective of the operative technique used, a further decline in median pressure to 35·0 (95 per cent c.i. 26·0–47·7) mmHg could be demonstrated* ($P < 0{\cdot}05$)*. This study indicates that anal sphincter pressure is reduced to a similar extent after hand-sewn and stapled anastomoses. Injury to the autonomic nervous supply to the anal sphincter mechanism might be the major cause for this reduction.*

The conventional technique for restorative proctocolectomy is colectomy combined with distal mucosal proctectomy, i.e. excision of the mucosa of the anorectum by an endoanal approach, followed by construction of an ileal reservoir anastomosed to the anal canal[1].

Although gross continence is fairly well preserved in these patients, minor functional defects are common, such as mucus and/or faecal leakage and an inability to release flatus safely. Many patients also suffer from skin soreness and need to wear a protective pad, particularly at night[2–4]. These functional imperfections are considered to be attributable partly to the significant and persistent decrease in resting anal pressure consistently found after surgery[5–9], but also to the loss of the anal transition zone, which is believed to play an important role in discriminatory function[10,11]. The precise cause of the postoperative reduction in sphincter pressure is not fully understood, but overdistension of the internal and external anal sphincters during endoanal mucosectomy has been considered a reasonable explanation[12,13].

Restorative proctocolectomy performed entirely from an abdominal approach, with transection of the rectal wall at the level of the levator ani muscles and construction of a circular stapled ileal pouch–anal anastomosis, is a novel alternative technique[14] that eliminates the need for anal dilatation. Evidence for improved functional results has been presented[15–17]. Although some studies have shown that there is no, or only moderate, reduction in resting anal pressure when using this technique[15,18–20], conflicting results have subsequently been reported by others[16,17,21]. These findings indicate that there is still a significant postoperative reduction in anal pressure despite the avoidance of dilatation, implying that factors other than sphincter overdistension and endoanal mucosectomy may be responsible for the deterioration in sphincter tone found after restorative proctocolectomy.

The principal aim of the present study was to investigate, by means of anal manometry, the changes in anal sphincter tone that occur during the different stages of restorative proctocolectomy, performed by either the conventional or modified stapling technique, and to follow the long-term effects on resting anal pressure in these patients.

Patients and methods

Patients

The study group comprised 24 consecutive patients, nine women and 15 men, with a median age of 35 (range 21–54) years, operated on for ulcerative colitis by restorative proctocolectomy with construction of a pelvic pouch and ileoanal anastomosis. The study was conducted in a randomized fashion using sealed envelopes. Twelve patients were randomized to the conventional technique with endoanal mucosectomy and 12 to operation with an abdominal approach and double stapling of the pouch–anal anastomosis. Fifteen patients had previously undergone colectomy as a first-stage operation, with either conventional ileostomy ($n = 13$) or ileorectal anastomosis ($n = 2$). There were no statistically significant differences in sex or age between the groups.

Surgical procedures

Patients were placed in the lithotomy position with the legs slightly elevated in Lloyd-Davies leg rests. General anaesthesia was induced with sodium thiopental 3–5 mg per kg body-weight. Atropine was given intravenously at a dose of 0·5 mg. A profound level of surgical anaesthesia with complete muscle relaxation was maintained by the use of nitrous oxide and oxygen (70:30) and repeated intravenous doses of fentanyl 0·1 mg and pancuronium bromide 1 mg.

All patients were operated on by a team of four senior surgeons adopting the same technique. The rectum was fully mobilized down to the pelvic floor. The superior rectal artery was divided at the sacral promontory. The presacral anatomical plane of dissection was entered posteriorly, including the mesorectum in the rectal excision. Great care was taken to preserve the presacral nerves, and both trunks were identified and carefully swept out of the operating field.

Conventional technique. A Parks' anal retractor was used for endoanal mucosectomy. Submucosal injection of a solution of adrenaline (1:300 000 in saline) facilitated excision of the mucosa, which was performed in four strips, starting at the dentate line and extended to a point a few centimetres above the pelvic floor. The rectal muscle wall was thereafter divided at this level via the abdominal approach.

The ileal pouch was fashioned according to the double-folding technique[22] and the pouch–anal anastomosis constructed with 16–20 interrupted absorbable sutures, grasping the full thickness of the bowel and including a part of the internal sphincter with the edge of the anoderm at the dentate line.

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Stapling technique. After full mobilization to the pelvic floor, the rectum was strongly retracted upwards and a transverse stapling instrument (RL30; Johnson and Johnson, Sollentuna, Sweden or TA30; Auto Suture Sverige, Kista, Sweden) applied across the anorectal junction. The level of transection was estimated at ≤2 cm above the dentate line by digital anal examination before firing.

After construction of the pouch as for the conventional procedure, the pouch–anal anastomosis was accomplished using a circular stapling device (Premium CEEA28; Auto Suture) introduced anally. The completed anastomosis was inspected using a fenestrated proctoscope and estimated to be located at a median of 1·7 (range 0·5–4·0) cm above the dentate line. Further details of operative technique are given by Hallgren *et al.*[17].

Manometry

Preoperative. Anal manometry was performed according to a technique described earlier[23] using the water-filled cuff of an endotracheal tube (Magill endotracheal tube 7·0 mm internal diameter; Mallinckrodt Laboratories, Athlone, Ireland) connected to a Statham transducer P23ID (Gould Medical, Oxnard, California, USA) and anal sphincter tone registered on a Grass model 7D polygraph (Grass Instruments, Quincy, Massachusetts, USA). Patients were examined in the left lateral position 2–4 days before surgery. Resting pressure was measured after at least 5 min adaptation to the probe.

Peroperative. Manometry was performed as described, apart from the position of the patient. The anal probe was inserted immediately after induction of anaesthesia and held in position by an assistant. Recordings were performed for about 5 min before and after each operative stage. The first recording (stage 1) was made after opening the abdomen. The second recording (stage 2) was performed after division of the superior rectal artery, the third (stage 3) after full mobilization of the rectum down to the pelvic floor and the fourth (stage 4) after completion of the pouch–anal anastomosis.

Postoperative. Anal manometry was carried out at follow-up before closure of the covering loop ileostomy, normally performed about 8 weeks after restorative proctocolectomy, and at 1, 3, 6 and 12 months after ileostomy closure.

Statistical analysis

For statistical comparison the Wilcoxon signed rank test or Mann–Whitney *U* test were used as appropriate. $P < 0.05$ was considered significant.

Results

Preoperative manometry

Median (95 per cent confidence interval (c.i.)) resting pressure 2–4 days before surgery was 63·0 (60·3–71·8) mmHg for all patients. The values were 60·0 (56·3–75·7) mmHg for patients randomized to mucosal proctectomy ($n = 12$) and 67·0 (58·5–75·8) mmHg for those in whom the stapling technique was subsequently employed ($n = 12$) (*Figure 1*). These values are not significantly different.

Peroperative manometry

The peroperative results are summarized in *Table 1*.

Stage 1. After induction of anaesthesia and opening of the abdomen, the median (95 per cent c.i.) sphincter pressure was 77·5 (69·9–83·3) mmHg. There was no significant difference between the conventional and stapled procedures (72·5 (62·4–82·1) *versus* 80·0 (72·0–92·6) mmHg).

Stage 2. Division of the superior rectal artery and the periarterial nerve fibres caused an immediate and marked drop in median (95 per cent c.i.) anal sphincter pressure (*Figure 2*), falling to 64·5 (55·2–70·0) mmHg ($P < 0.01$), corresponding to a 17 per cent reduction, with a decrease from 72·5 to 60·0 (48·4–69·6) mmHg in the conventional group and from 80·0 to 72·0 (55·3–80·4) after the stapled procedure.

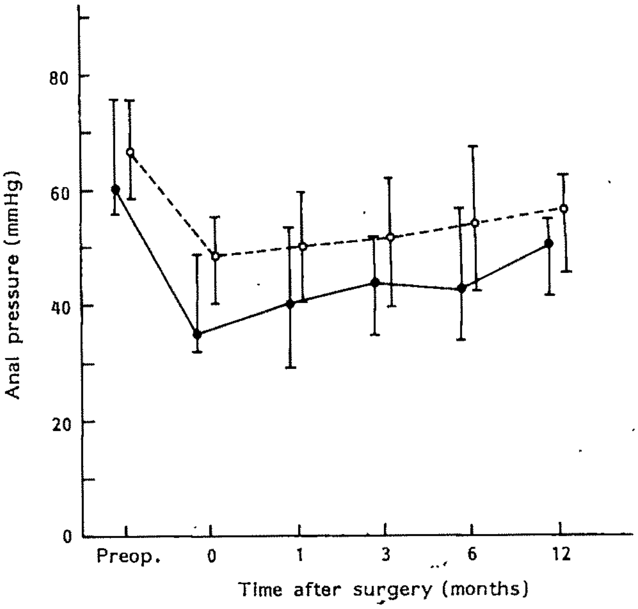

Figure 1 *Median (95 per cent confidence interval) resting anal sphincter pressure before operation and at intervals during follow-up for patients operated on using the hand-sewn (●) or stapled (○) technique*

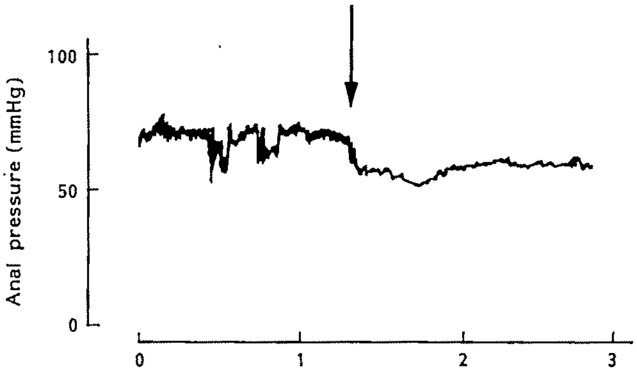

Figure 2 *Anal pressure reduction, amounting to about 20 per cent, after division of the superior rectal artery (arrow). Note the immediate pressure drop*

Table 1 *Resting anal sphincter pressure at different stages of the operative procedure*

	Resting anal pressure (mmHg)			
Operating technique	After induction (stage 1)	Superior rectal artery divided (stage 2)	Complete rectal mobilization (stage 3)	Anastomosis complete (stage 4)
Hand-sewn	72·5 (62·4–82·1)	60·0 (48·4–69·6)	50·0 (38·7–57·1)	31·0 (11·9–62·1)
Stapled	80·0 (72·0–92·6)	72·0 (55·3–80·4)	51·0 (36·7–59·3)	35·0 (23·2–50·4)
Total	77·5 (69·9–83·3)	64·5 (55·2–70·0)	50·0 (40·1–53·5)	35·0 (26·0–47·7)

Values are median (95 per cent confidence interval)

Stage 3. After complete dissection of the rectum down to the pelvic floor, with division of the lateral ligaments, a further drop in median (95 per cent c.i.) sphincter pressure from 64·5 to 50·0 (40·1–53·5) mmHg ($P < 0.01$) was recorded, corresponding to a 22 per cent reduction. In the conventional group of patients the value decreased to 50·0 (38·7–57·1) mmHg and to 51·0 (36·7–59·3) mmHg in the stapled procedure at this stage of the operation.

Stage 4. After complete endoanal mucosectomy and manual suturing of the pouch–anal anastomosis or after transection of the rectal wall and stapling of the anastomosis, the median (95 per cent c.i.) anal sphincter pressure in the conventional group decreased from 50·0 to 31·0 (11·9–62·1) mmHg ($P < 0.05$) and in the stapled group from 51·0 to 35·0 (23·2–50·4) mmHg ($P < 0.05$). The reduction in sphincter tone was similar in the two groups. The anal pressure at this stage was about 43 per cent of the stage 1 value in the conventional group and 44 per cent in the stapled group.

Postoperative manometry

A gradual improvement in resting pressure was demonstrated with the passage of time (*Figure 1*). At 6 months after closure of the loop ileostomy, the median (95 per cent c.i.) value was 43·0 (33·7–59·0) mmHg in the hand-sewn group and 53·5 (42·6–68·2) mmHg in those undergoing stapling. At 12 months values were 50·0 (41·8–55·3) and 56·0 (46·5–63·1) mmHg respectively, still representing a persistent reduction of 17 and 16 per cent compared with preoperative pressures ($P < 0.05$).

Discussion

It is commonly held that trauma to the internal anal sphincter (IAS), resulting from anal dilatation necessary for endoanal mucosectomy and anastomotic construction, is the principal cause of sphincter dysfunction after restorative proctocolectomy using the conventional technique. Proctectomy performed entirely from an abdominal approach, without endoanal instrumentation apart from insertion of the stapling device, is believed to preserve sphincter function with maintenance of a normal anal canal and improvement of functional results. Although findings from most previous studies support this view, diverging results have been reported by Williams *et al.*[16] and in studies from this unit[17]. These suggest that sphincter trauma is not the major cause of dysfunction and that other mechanisms, such as injury to the autonomic nervous pathways regulating sphincter tone, may be involved. This view is strongly supported by the present study, which demonstrates that IAS pressure was reduced to a similar extent in patients undergoing the conventional technique and in those operated on with stapling. In both series the anal pressure was reduced in a sequential manner during the surgical procedure, with an immediate decrease in pressure on severing the superior rectal artery, a further reduction after full mobilization of the rectum, followed by another equally large drop at the final stage after construction of the anastomosis by either technique.

According to traditional physiology there are two separate extrinsic sympathetic nerve fibre sets supplying the pelvic organs[24–27]: the hypogastric nerves, also known as the presacral nerves in humans, and the lumbar colonic nerves, which are easily distinguished in both the cat and dog. These fibres are less obvious in man where they correspond to the periarterial nerve fibres (inferior mesenteric nerve), originating from the inferior mesenteric plexus running distally along the inferior mesenteric and superior rectal arteries.

Gaskell[28] proposed in 1920 that sympathetic adrenergic fibres in the cat are inhibitory to the gut, but exert a strong excitatory influence on anal sphincter tone, a view supported by studies in humans, where profound reduction in anal pressure has been reported after high spinal and epidural anaesthesia, which block the sympathetic outflow to the IAS[29,30]. Pharmacological studies in humans have shown that autonomic control of the IAS seems to be mediated by a complex interplay of excitatory and inhibitory influences[31,32].

Resting anal pressure is produced largely by tonic contraction of the IAS maintained by a combination of neurogenic and myogenic activity[33,34]. Approximately 50 per cent of the resting pressure depends on a dual tonic sympathetic discharge via the lumbar colonic and hypogastric nerves[35]. Damage to either one or both sets of these nerves could possibly explain the reduction in IAS pressure after surgery. Since the lumbar colonic nerves are contained in the vascular pedicle in the sigmoid and rectal mesentery, complete transection of these nerves is inevitable during proctocolectomy, especially when the superior rectal artery is divided and the mesorectum included in the rectal excision. In the present study division of the lumbar colonic nerves (stage 2) induced a decrease in resting pressure amounting to about 17 per cent, a reduction similar to that reported in an experimental study by Carlstedt *et al.*[35]. This agreement in the magnitude of reduction in resting pressure between the present study and animal experiments is striking and is also consistent with findings after low anterior resection of the rectum in humans[36].

The hypogastric nerve descends into the pelvis, dividing into two branches which separate to pass to either side of the pelvis. These follow the lateral pelvic walls and join the pelvic parasympathetic nerves in the lateral ligaments and/or on the superior aspect of the pelvic diaphragm to form the pelvic plexus[37,38]. Even if, as in the present study, the hypogastric nerves are identified when entering the anatomical presacral space and carefully swept out of the operative field, their distal connection to the IAS may well be damaged during the close perimuscular dissection of the rectum at the level where the lateral ligaments are divided and Denonvilliers' fascia is incised. The significant reduction in resting pressure observed after complete dissection of the rectum down to the pelvic floor would support this assumption. The final recording showed a significant further decrease in pressure, which represents a combination of the effects of transection of the bowel wall and construction of the anastomosis. In the stapled technique it is more likely that transection of the bowel is the major cause for this reduction, since stapling itself is not likely to induce any substantial sphincter damage.

The influence of the parasympathetic pelvic nerves on IAS function is still controversial. Carlstedt *et al.*[39] demonstrated that, in the cat, division of the pelvic nerves did not significantly influence resting anal pressure, indicating either that there is no tonic discharge in the pelvic nerves to the IAS or that a balance exists between excitatory and inhibitory neurones. Frenckner and Ihre[29] found minor changes in resting pressure after low spinal anaesthesia in humans, which selectively blocks the parasympathetic nerves. There are, however, studies reporting a reduction in anal tone in the cat after division of the pelvic nerves[40], and a human study of individuals with meningocele (theoretically devoid of parasympathetic pathways, but having sympathetic outflow) reported reduced anal tone compared with healthy controls[41]. Since the parasympathetic innervation of the IAS is not completely clear, it is uncertain to what extent it may also be damaged during operation.

A similar study of patients who underwent low anterior resection for cancer[42] was designed to determine whether intraoperative injury to the anal sphincter or its nerve supply could be detected. The results of the present paper are at variance with that study, which demonstrated that 'full mobilization of the rectum is possible without injury to the presacral innervation of the internal anal sphincter'. Horgan *et al.*[42] found that division of the inferior mesenteric artery, and full mobilization and transection of the rectum did not cause a reduction in resting pressure, while a significant decrease was recorded after construction of the colorectal anastomosis with the CEEA instrument. However, their results are in many respects incomplete and difficult to interpret and there may be several explanations for the divergent conclusions. For example, the mean resting pressure of 33 mmHg, reflecting a low prevailing sphincter tone, may well mask any inhibitory effects of subsequent nerve transection. Moreover, in the present study the recording device was held in a firm position by an assistant during the operative procedures, whereas in that of Horgan *et al.* the endotracheal tube was sutured to the perineal skin, making positional changes possible. Apart from other differences in methodology, discrepancy in age and diagnosis of the patients may also contribute to the contradictory findings.

The results from the present study indicate that damage to the autonomic nerve supply of the IAS may be the major cause of reduction in resting pressure. Damage to the extrinsic sympathetic supply to the IAS has also been suggested to be of primary pathogenic importance in patients with idiopathic faecal incontinence and reduced pressure[32]. As no statistically significant difference in the intraoperative decrease in anal pressure between the two methods of construction of the anastomosis was found, it may be assumed that anal instrumentation and concomitant sphincter dilatation did not add significant sphincter damage in the acute phase. This assumption is supported by the finding that a significant and similar reduction in sphincter pressure was present in the two groups even 1 year after surgery, indicating a permanent sphincter defect in both. It is, however, not possible to rule out peroperative sphincter dilatation as one reason for this long-term effect, but the concordance in pressure between the two methods suggests that nerve damage is the major cause.

The divergence in results from this and other centres with regard to postoperative resting pressure after stapling of the pouch–anal anastomosis[15–17,20,21,43,44] may result from differences in methodology or from variation in the extent of rectal dissection and/or level of transection of the anorectum, where less extensive dissection or division of the rectum at a high level above the dentate line may leave some of the innervation to the IAS undisturbed. Moreover, variation in follow-up, and differences in criteria of assessment and grading for functional imperfections may contribute to discrepancies in evaluation and comparison of results.

Prevailing data support the use of the stapling method for its simplicity and safety and also, to some extent, for a superior functional result. However, these apparent advantages must be balanced against possible disadvantages. One of the major objects of the conventional technique of restorative proctocolectomy, both for the treatment of ulcerative colitis and of familial adenomatous polyposis, is the complete eradication of all diseased mucosa. This cannot be achieved when the pouch is stapled to the top of the anal canal since at least 1–2 cm of anal mucosa is preserved with this technique. Many surgeons performing the operation from above are tempted to construct the anastomosis at too high a level, making this disadvantage more pronounced; this technique cannot be recommended. It has yet to be established whether the stapling technique is justified, in view of the risk of epithelial dysplasia and malignant transformation with the passage of time. This risk is of particular importance in patients with polyposis.

It is concluded from the results of the present study that damage to the autonomic nervous supply to the IAS may well be the principal cause of the reduction in resting anal pressure that is invariably seen after restorative proctocolectomy, and that anal sphincter tone is permanently reduced to the same extent even when proctectomy is performed entirely from an abdominal approach, avoiding dilatation of the anal canal.

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Oestrogen and progesterone receptors in colorectal cancer and human colonic cancer cell lines

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Receptors for oestrogen (ER) and progesterone (PR) were assayed in tissue from 17 patients with colorectal cancer and five colonic cancer cell lines using enzyme immunoassays. ERs and PRs were detected in 15 and 17 cancers respectively, although the levels detected were low: median (range) ER 1·3 (0–11·3) and PR 3·9 (0·3–10·2) fmol per mg protein. These values were not significantly different from median (range) levels of ER (1·1 (0·6–3·0) fmol/mg) and PR (1·9 (0·5–3·2) fmol/mg) detected in normal mucosa. There were significant positive correlations between the levels of ER and PR for cancer tissue ($\tau = 0{\cdot}56$, $P < 0{\cdot}005$; r(*log transform*) $= 0{\cdot}68$, $P < 0{\cdot}003$; $n = 17$) *but not for mucosa, and between levels of ER in cancer tissue and mucosa* ($\tau = 0{\cdot}55$, $P < 0{\cdot}05$; r(*log transform*) $= 0{\cdot}70$, $P < 0{\cdot}025$; $n = 10$) *but not between the corresponding PR values. In maintenance media, which contained phenol red and unstripped fetal calf serum, the median (range) concentration of ER was 1·9 (1·2–10·4) fmol/mg and that for PR 24·3 (9·1–63·2) fmol/mg in the five cell lines studied (HT-29, LS174T, SW620, LoVo, COLO 320DM). The addition of oestradiol (10 nmol/l) to phenol red-free medium containing 5 per cent dextran-coated charcoal-treated fetal calf serum had little effect on the concentration of ERs or PRs in SW620, LoVo and COLO 320DM cells after 7 days' culture. It is concluded that ERs and PRs are expressed in malignant and normal colonic mucosa. ERs appear to be a feature of the colonic mucosa rather than the malignant process, but in carcinoma may regulate synthesis of PRs, suggesting a degree of oestrogen responsiveness.*

Proximal colonic cancer is more common in women than men at all ages; at more distal sites this holds true only before the menopause[1,2]. The incidence of rectal cancer is similar in both sexes at younger ages, but the disease predominates in men later in life[1]. This crossover effect of male and female incidence rates in distal colonic cancer may result from the protective effect of pregnancy[3–5]. Several mechanisms have been proposed to explain this, including hormone influences on bile acid metabolism[2], physical activity associated with large families[6] and 'as yet unidentified life style factors associated with having children'[7].

There is a positive association between the incidence of cancer of the breast and colon in some studies[8,9]. Although breast cancer is associated with other extramammary tumours, the predominant site is the colorectum[10], leading to the suggestion that the two tumours may have aetiological factors in common[9]. It is possible, however, that hormones may have a direct effect on colonic mucosa that ultimately lowers the risk of more distal colonic cancer in women.

Steroid receptors are a prerequisite for hormone responsiveness and a number of investigators have attempted to identify such receptors in colonic tissue. Receptors for oestrogen (ER) and progesterone (PR) have been found in both cancerous[11–20] and normal[15,16,18,20] colonic mucosa, although some studies have failed to identify receptors in significant amounts or in a substantial proportion of cases[21–23]. This inconsistency may reflect differences in assay methods. Both receptors have been identified in colorectal tumour cells by a fluorescent cytochemical technique[19] and a recent study reported messenger RNA for the ER in colonic mucosa and tumours[24].

The PR is one of the proteins whose synthesis is regulated by oestrogens, and in breast cancer functional and activated ERs are associated with induction of PRs[25,26], although this relationship has not previously been investigated in colorectal cancer. In this study, expression of ER and PR proteins has been investigated by enzyme immunoassay in malignant and normal colorectal tissue and in five human colonic cancer cell lines, to assess whether any correlation exists between the two types of receptor and their sites of expression.

Patients and methods

Tissue

Tumour specimens from 17 patients with colorectal cancer (six men, 11 women) were analysed, together with paired normal mucosa (10 cm from the tumour) from ten of these patients. The mean age was 69 (range 50–80) years. Sites were: rectum, six; rectosigmoid, two; sigmoid, six; ascending colon, one; and caecum, two. One cancer was Dukes' A, eight Dukes' B and eight Dukes' C. Two lesions were well differentiated, 14 moderately differentiated and one poorly differentiated.

Representative samples of the tumour and normal mucosa were taken immediately after removal of the specimen at operation and placed in 20 mmol/l HEPES buffer (pH 7·4) containing 0·25 mol/l sucrose, 1·5 mmol/l $MgCl_2$ and 50 per cent glycerol, and stored at −20°C for up to 3·5 months, except for one tumour that was assayed after 7 months' storage. This method[27] was originally shown to preserve steroid receptors in breast tumour for at least 3 months, the maximum period studied. In fact, receptor levels in breast tumours are conserved for at least 1 year in this sucrose–glycerol buffer (*Table 1*).

The colon tissue (median 260 (range 120–360) mg) was homogenized using an Ultraturrax (model T18/10; Sartorius, Epsom, UK) for three 10-s bursts at near maximum speed in 1–2 ml 10 mmol/l

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HEPES (pH 7·4) containing 0·4 mol/l KCl, 1·5 mmol/l ethylenediamine tetra-acetic acid (EDTA), 5·0 mmol/l sodium molybdate, 10 per cent glycerol and 0·5 mmol/l dithiothreitol. After centrifugation at 2000*g* for 10 min and 5000*g* for 30 min at 4°C, the supernatant or 'whole cell extract' was used to assay ERs and PRs. This procedure ensures that most of the nuclear-bound steroid receptor protein is extracted into the soluble fraction of the homogenate[28,29].

Human colonic cancer cell lines

The five cell lines studied were HT-29, LS174T, SW620, LoVo and COLO 320DM (ATCC). All lines were maintained in serum-containing media that included phenol red: HT-29 in RPMI 1640 with 10 per cent fetal calf serum (FCS); LS174T in Dulbecco's modified Eagle's (DME) with 15 per cent FCS; SW620 in L-15 with 10 per cent FCS: LoVo in Ham's F12 with 10 per cent FCS; and COLO 320DM in RPMI 1640 with 10 per cent FCS. All media were supplemented with 2 mmol/l glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin; the medium for LS174T also contained 1 mmol/l non-essential amino acids. In one series of experiments the five cell lines were plated out (10^6 cells) in 75-cm^2 flasks and grown in maintenance medium for 7 days. In a separate series SW620, LoVo and COLO 320DM (10^6 cells) were plated out and grown in oestrogen-depleted medium comprising phenol red-free DME–F12 (50:50, vol:vol) containing 5 per cent dextran-coated charcoal-treated FCS, all the above supplements plus 1 μg/ml human insulin, with or without 10 nmol/l oestradiol, with a medium change every 2–3 days for 7 days. At the end of both series of experiments the cells were washed with phosphate-buffered saline, harvested with trypsin–EDTA, washed twice with medium containing FCS and phosphate-buffered saline and cell counts determined from an aliquot of the cell suspension using a haemocytometer. The cell pellets were homogenized as described above for colon tissue before assay for ERs and PRs.

Table 1 *Oestrogen receptor levels in breast tumours stored in sucrose–glycerol buffer at −20°C*

	Time after biopsy (days)		Oestrogen receptor concentration (fmol/mg)	
Tumour no.	First assay	Second assay	First assay	Second assay
1	4	62	50	55
2	7	65	109	122
3	20	68	57	26
4	12	76	95	66
5	19	83	31	96
6	13	90	76	71
7	27	182	63	69
8	6	217	151	203
9	62	363	21	23
10	70	364	47	84

Steroid receptor assays

ER and PR levels were determined by enzyme immunoassay (Abbott Diagnostics, Maidenhead, UK). As is routine in this laboratory, a detection limit of 3 fmol per ml extract was used for both assays, being approximately twice the sensitivity given in the kit protocol. Although the assay procedure has the sensitivity quoted by the manufacturer (2 s.d. above zero standard), the detection limit chosen represents the lowest level of receptor protein that can be reliably and consistently recorded in tissue extracts, allowing for the precision of the method at low receptor concentrations. A high ratio of tissue weight to homogenizing buffer volume was adopted in this study to prepare 'concentrated' supernatants (i.e. high protein concentrations) in an attempt to obtain levels of receptor protein above the assay detection limit. The precision of the assays for breast tumours with receptor levels <100 fmol/ml in this laboratory is 8 per cent for ERs and 9 per cent for PRs; equivalent values for MCF-7 cells are 5 and 6 per cent respectively.

Protein assay

The protein content of the supernatant was quantified using an assay (Bio-Rad, Hemel Hempstead, UK) based on that of Bradford[30].

Statistical analysis

Values for levels of ER and PR, expressed as femtomoles per millilitre or per milligram extract, are given as median (range). Differences were analysed by the two-tailed Mann–Whitney U test and correlations by Kendall's rank correlation test (τ), with correction for ties, or Pearson's linear correlation for log-transformed data. $P < 0·05$ was considered significant.

Results

Human tissue

The median protein content of whole cell extracts used in the assay was 9·6 (range 2·7–18·5) mg/ml.

Table 2 *Oestrogen and progesterone receptor levels in colorectal tumours and adjacent normal mucosa*

				Oestrogen receptor concentration				Progesterone receptor concentration			
				fmol/ml		fmol/mg		fmol/ml		fmol/mg	
Patient no.	Sex	Site	Dukes' class	Tumour	Mucosa	Tumour	Mucosa	Tumour	Mucosa	Tumour	Mucosa
1	F	Sigmoid	B	14·7	21·2	1·5	2·3	44·4	4·7	4·5	0·5
2	F	Sigmoid	C	17·6	24·0	2·6	2·5	35·9	10·8	5·4	1·1
3	F	Caecum	C	5·9	8·5	0·6	1·0	3·2	12·2	0·3	1·4
4	F	Rectum	C	10·6	22·3	1·4	3·0	29·0	15·1	3·9	2·0
5	M	Rectum	C	15·9	5·2	1·5	0·6	13·1	20·8	1·2	2·4
6	M	Ascending colon	B	13·2	19·2	1·2	1·6	7·9	37·4	0·7	3·2
7	F	Sigmoid	C	5·7	10·3	0·6	0·9	4·3	20·6	0·4	1·8
8	M	Caecum	B	5·7	6·2	0·3	0·6	19·9	12·2	1·1	1·1
9	F	Rectum	A	2·4*	7·8	0·0*	0·7	42·9	30·1	4·4	2·6
10	F	Rectum	B	16·9	13·7	1·1	1·2	15·8	26·4	1·0	2·3
11	M	Rectum	B	4·9	—	1·1	—	21·3	—	4·6	—
12	F	Rectum	B	19·1	—	5·5	—	23·9	—	6·9	—
13	F	Rectosigmoid junction	B	30·9	—	11·3	—	27·8	—	10·2	—
14	M	Sigmoid	B	12·9	—	4·3	—	15·7	—	5·2	—
15	F	Sigmoid	C	2·3*	—	0·0*	—	4·2	—	0·8	—
16	F	Sigmoid	C	12·2	—	1·4	—	19·2	—	2·3	—
17	M	Rectosigmoid junction	C	12·3	—	1·3	—	46·8	—	4·8	—

*Assay was below the detection limit of 3 fmol/ml; zero assigned to fmol/mg value

ERs and PRs were expressed in both colorectal cancer and normal tissue at low levels (*Table 2*). ERs were detected in 15 (88 per cent) of 17 tumours (range 4·9–30·9 fmol per ml extract). PRs were detected in all 17 tumours (3·2–46·8 fmol/ml). ERs (5·2–24·0 fmol/ml) and PRs (4·7–37·4 fmol/ml) were detected in all samples of normal mucosa. The median (range) receptor levels in tumours ($n = 17$) were 1·3 (0–11·3) fmol per mg protein for the ER and 3·9 (0·3–10·2) fmol/mg for the PR; in 11 of 17 tumours the levels of PR were greater than those of the ER. In normal mucosa ($n = 10$) median (range) levels of ERs and PRs were 1·1 (0·6–3·0) and 1·9 (0·5–3·2) fmol per mg protein respectively; in seven of ten cases the concentration of PRs was greater than that of ERs. There was no significant difference in the expression of either ERs or PRs between tumours and paired normal mucosa ($n = 10$), between men and women, or between Dukes' B or C tumours.

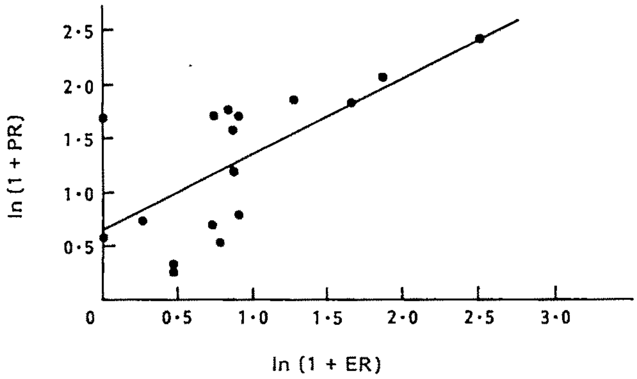

Figure 1 *Relationship between log-transformed (ln(1 + x)) oestrogen (ER) and progesterone (PR) receptor concentrations expressed as femtomoles per milligram protein in colorectal cancer.* ($r = 0·68$, $P < 0·003$; $n = 17$)

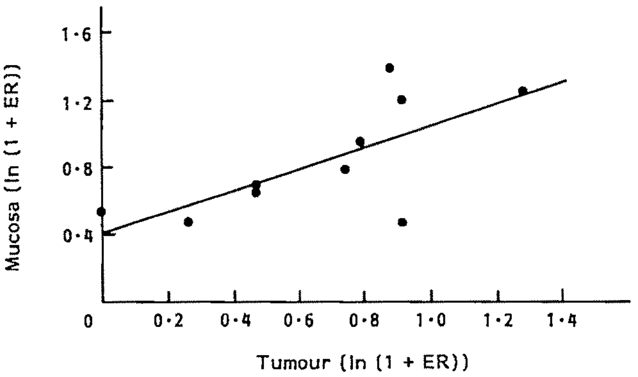

Figure 2 *Relationship between log-transformed (ln(1 + x)) oestrogen receptor (ER) concentration expressed as femtomoles per milligram protein in tumour and mucosa.* ($r = 0·70$, $P < 0·025$; $n = 10$)

There were significant positive correlations between tumour levels of ER and PR ($\tau = 0·56$, $P < 0·005$; $n = 17$) and between levels of tumour ER and mucosal ER ($\tau = 0·55$, $P < 0·05$; $n = 10$). Both of these relationships exhibited significant linear correlations after log transformation ($r = 0·68$, $P < 0·003$; *Figure 1*; $r = 0·70$, $P < 0·025$; *Figure 2*, respectively). There was no correlation between mucosal levels of ER and PR ($\tau = -0·11$) or between levels of mucosal and tumour PR ($\tau = -0·14$).

Colonic cancer cell lines

ERs and PRs were detected in all cell lines (*Table 3*). In maintenance media, ERs were detected at levels ranging from 1·2 to 10·4 fmol/mg and PRs at 9·1–63·2 fmol/mg. The presence of 10 nmol/l oestradiol in phenol red-free medium containing oestrogen-depleted FCS did not appear to downregulate ERs or induce PRs in SW620, LoVo or COLO 320DM cell lines, whether receptor values were expressed per milligram protein or per 10^6 cells (*Table 3*). Levels of PR were greater than those of ER for all cell lines and culture conditions whether receptors were expressed per milligram protein or per 10^6 cells.

Discussion

In the present study, ERs and/or PRs were detected in all colorectal cancer specimens and normal mucosa samples studied, albeit at low levels when expressed per milligram protein. None of the tumours expressed receptor protein at a level that would have been positive by criteria used for breast tumours in the authors' laboratory (≥20 fmol/mg). This finding is in agreement with the results of some published studies[21–23] but not with those of others[11–20] where lower cut-off levels were used to indicate receptor positivity. Colorectal tumour receptor positivity in these reports varies from 14 to 83 per cent for ERs and from 7 to 50 per cent for PRs. In some studies values were high enough to suggest endocrine dependence[13,17].

The lack of correlation between levels of ERs and sex or Dukes' class is consistent with previous studies, which also found no relationship with age, histological grade or location of the tumour[11,15,16,18]. The latter observation suggests that the lower incidence of distal colonic and rectal cancer in

Table 3 *Oestrogen and progesterone receptor levels in colonic cancer cell lines*

				Oestrogen receptor concentration		Progesterone receptor concentration	
Cell line	Culture conditions	Total cells (×10^6)	Protein concentration (μg per 10^6 cells)	fmol/mg	fmol per 10^6 cells	fmol/mg	fmol per 10^6 cells
HT-29	Maintenance	40·0	81	1·6	0·1	9·1	0·7
LS174T	Maintenance	28·2	91	1·2	0·1	24·3	2·2
SW620	Maintenance	60·0	49	2·4	0·1	22·0	1·1
SW620	EDM	38·3	79	1·8	0·1	12·1	1·0
SW620	EDM + E_2	24·3	54	3·5	0·2	14·5	0·8
LoVo	Maintenance	8·6	74	10·4	0·8	30·2	2·2
LoVo	EDM	3·6	111	9·0	1·0	27·8	3·1
LoVo	EDM + E_2	4·2	81	11·8	1·0	22·1	1·8
COLO 320DM	Maintenance	35·2	70	1·9	0·1	63·2	4·4
COLO 320DM	EDM	8·4	114	4·7	0·5	25·5	2·9
COLO 320DM	EDM + E_2	8·5	113	6·1	0·7	25·3	2·9

EDM, oestrogen-depleted medium; E_2, 10 nmol/l oestradiol added postmenopausal women is not related to the concentration of ERs.

Most studies of colorectal cancer have used the steroid-binding assay with a dextran-coated charcoal procedure, but conflicting results have been obtained. Three previous reports used enzyme immunoassay to assess the level of ERs in colorectal tumours[12,21,23] but only one quantified both receptors[12], and this showed the levels of the PR to be lower than those of the ER and less often above the cut-off for positive status. Low concentrations of ERs (negative status) were noted in two of these studies[21,23], which is consistent with the present findings, although receptor concentration in femtomoles per millilitre tumour homogenate was not reported. The enzyme immunoassay methods for determination of ERs and PRs are specific and sensitive, but nevertheless require sufficient tissue to enable low receptor levels to be detected, hence the use of concentrated homogenates. The present study is the first to report the presence of ERs and PRs determined by enzyme immunoassay in both tumour and paired normal mucosa.

ERs and PRs were detected in normal mucosa in all cases at levels similar to those in tumours. ERs and PRs have been detected previously in normal colonic mucosa using radioligand binding methods[15,16,18,20]. These studies failed to find a difference in levels of ER or PR between tumour and mucosa, and the present data are in agreement with this. However, a significant correlation between levels of ERs in tumours and paired normal mucosa was observed in the present study, a finding which suggests that receptor levels expressed in tumours may be a reflection of the receptor status of the surrounding colonic mucosa, and that expression of ERs is a feature of colonic mucosa rather than a property of colonic mucosal cells that have become neoplastic. To the authors' knowledge, this relationship has not been noted before, and it was not observed for PRs.

In common with previous studies[15,16,18], mucosa adjacent to the tumour (10 cm distant) was used in the present study to represent normal colonic tissue for steroid receptor measurement. The use of 'normal' mucosa from the same patient allows for control of potential confounding variables such as parity, drug treatment and diet, which would be difficult to control for if mucosa from patients with benign conditions were used, although even then the 'normality' of the mucosa would not be certain. The adjacent normal mucosa may have been subjected to the same carcinogenic influences as the tumour, although this effect has not been expressed as histological change. In any event, the nature and mode of action of the carcinogens are unknown, and there is no certainty that all mucosal cells have been exposed. At present, there are no grounds for believing that histologically normal tissue would not have normal levels of steroid receptors.

The level of PRs in femtomoles per milligram was higher than that of the ER in 65 per cent of tumours, 70 per cent of normal mucosal specimens and all the colonic cancer cell lines. This tendency for levels of PRs to be higher than those of ERs in colorectal tumours has been noted by some workers[19,22], while others have reported that the concentration of PRs is lower[12,15,16,20]. The higher levels of the PR, and the significant correlation between levels of ERs and PRs in tumours, suggest that ERs in colorectal cancer tissue may be active and producing oestrogen-regulated proteins such as the PR[25,26], although this hypothesis requires further study. Sica *et al.*[13] alluded to a similar relationship, although no correlational analysis was carried out. In the present study no correlation was found between mucosal levels of ERs and PRs, implying that the above relationship holds only for tumour tissue. This apparent change in regulatory function may be an important feature in the development and/or growth of colorectal tumours.

Both steroid receptors were detected in all the human colonic cancer cell lines studied. This is believed to be the first paper to report both ERs and PRs in these cell lines. Levels of PRs were usually >20 fmol/mg and were greater than levels of ERs in all cell lines. The addition of 10 nmol/l oestradiol to oestrogen-depleted medium did not appear to downregulate ERs or induce PRs. While this concentration of oestradiol is optimal for stimulation of MCF-7 human breast cancer cells, colonic cancer cells may require higher levels of oestrogen, or indeed another ligand, to regulate the ER. In this context it is interesting to note a recent observation of the authors that bile acids, to which the colon is naturally exposed, have oestrogen-like activity on the ERs of MCF-7 cells[31].

In conclusion, ERs and PRs are present in colorectal tumours, normal mucosa and human colonic cancer cell lines at low levels. The concentration of neither receptor is significantly raised in tumours although more substantial levels of the PR were found in the cell lines. It appears that levels of ERs in tumours are related to those in normal mucosa and may not be a feature of the malignant process. However, ERs in tumours, but not normal mucosa, may be functional and regulatory for the PR, suggesting some degree of potential oestrogen responsiveness.

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Case report

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'Car-crusher colon'

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An unusual hazard of sleeping rough, together with an interesting traumatic injury to the large intestine, is reported.

Case report

A 30-year-old unemployed labourer with a current problem of heroin abuse was admitted in the early afternoon. He was in the habit of sleeping rough in a car-breaker's yard and had previously escaped any trauma. While asleep in one of the vehicles in the yard, the man was awakened by the jaws of a vehicle grab that seized his abdomen in the anteroposterior axis. The man's cries of pain were sufficient to alert the operator of the vehicle crane and he was transferred to hospital by ambulance.

On arrival the patient complained of severe generalized abdominal pain that was most intense on the left side. On examination he was normotensive with a pulse rate of 100 beats/min. Injuries were confined to the abdomen, with severe bruising and grazing to the left upper aspect. The patient had generalized tenderness and left upper quadrant guarding, together with absent bowel sounds. A presumptive diagnosis of ruptured viscus was made. Emergency abdominal ultrasonography performed shortly after admission revealed no rupture of the liver or spleen but identified a haematoma within the peritoneal cavity. Laparotomy was performed, at which a 15-cm rupture of the abdominal wall musculature was found extending from the lateral border of the left rectus abdominis through the oblique abdominal muscles and peritoneum. The mesocolon of the left transverse and upper descending colon was torn. A 30-cm segment of colon in this region displayed two separate areas roughly 7 cm long in which the muscle coats had been degloved to reveal an intact tube of large bowel mucosa. Although bruised, the bowel between these areas was intact. Left hemicolectomy with primary anastomosis was performed together with repair of the ruptured abdominal musculature. The patient made a steady recovery and left hospital 3 weeks after injury.

Discussion

The circumstances of this case could have appeared in a best-selling film. Clearly the outcome would have been much more final had the grab operator not been alerted. This fact alone is remarkable in an environment that is dominated by noise, and is testament to the severity of the patient's suffering. The injury to the large bowel is also remarkable. Degloving of the skin from limbs is familiar following shear forces but to our knowledge no such degloving event has been reported in the layers of the large bowel, although the mode of injury is certainly by 'shear'. The moral of the tale is surely to choose one's sleeping place with care.

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Surgical Research Society Abstracts

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The following abstracts were presented at the 77th meeting of the Surgical Research Society, with Professor L. E. Hughes in the chair. The meeting was held on 7–8 January 1993 at the Charing Cross and Westminster Medical School, London. One hundred and nine papers were presented during the scientific sessions, which were preceded by a symposium entitled 'Duplex scanning and B-mode ultrasound in current vascular diagnosis with live demonstrations'. The Patey Prize was awarded to Mr I. S. Paterson for his paper entitled 'Pulmonary trapping of activated neutrophils following aneurysm repair'.

Role of immunomodulatory cytokines in the acute septic response

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The macrophage plays a pivotal role in the immune response to infection. The effects of macrophage-activating cytokines (interferon (IFN) γ and interleukin (IL) 4) and their monoclonal antibodies in modulating host response to intra-abdominal sepsis were examined. Mice were given IFN-γ, IL-4, control antibody, anti-IFN-γ or anti-IL-4.

In study 1, mice ($n = 15$ per group) received endotoxin (lipopolysaccharide; LPS) (60 mg kg^{-1}) and 2 h later cytokine (10^4 units) or monoclonal antibody (200 μg). In study 2, mice ($n = 16$ per group) received *Escherichia coli* (33×10^6) and were randomized to the same treatment groups. In study 3, mice ($n = 15$ per group) were subjected to caecal ligation and puncture; they were randomized to the same treatment groups and studied for median survival. In study 4, mice ($n = 15$ per group) were subjected to caecal ligation and puncture and received cytokine (10^4 units) or monoclonal antibody (100 μg) over 3 days in divided doses. Percentage survival rates were:

Study	IFN-γ	IL-4	Control	Anti-IFN-γ	Anti-IL-4
1	47	—	33	100*	—
2	25	—	0	65*†	—
3	7	0	0	27‡§	0
4	25	27	24	31	63ǂ

*$P < 0·01$ *versus* other groups, †$P < 0·05$ *versus* IFN-γ (χ^2 test); ‡$P = 0·01$ *versus* IFN-γ, §$P < 0·01$ *versus* control, ǂ$P < 0·05$ *versus* control and IL-4 (log rank test)

IFN-γ and IL-4 were not protective when given 2 h after LPS, *E. coli* or caecal ligation and puncture. Anti-IFN-γ offered significant protection against LPS, *E. coli*, and caecal ligation and puncture (single dose). Bolus anti-IL-4 was not protective against caecal ligation and puncture, but divided dosage significantly enhanced survival. Treatment with monoclonal antibodies against IFN-γ and IL-4 was protective against intra-abdominal sepsis, presumably by inhibiting excessive macrophage activation.

Metabolic changes after laparoscopic and minilaparoscopic cholecystectomy: a randomized trial

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The magnitude of the metabolic response to injury has been shown to be proportional to the degree of surgical trauma. Laparoscopic surgery is said to result in less surgical trauma than the open technique.

The aim of this randomized study was to compare the metabolic response to injury after laparoscopic cholecystectomy (LC; $n = 10$) and minilaparoscopic cholecystectomy with a 5–7-cm incision (MC; $n = 10$). Venous blood samples were taken 0, 3, 6, 9, 12, 18, 24, 48, 72 and 168 h after surgery and analysed for C-reactive protein, interleukin 6, cortisol, albumin, transferrin, iron, fibrinogen, fibrin degradation products (FDPs), polymorphonuclear (PMN) elastase, neutrophils and lymphocytes. Urine samples at 24 h were analysed for urea, creatinine, 3-methylhistidine and catecholamines. The magnitude of the metabolic changes from baseline levels was quantified by calculating areas under individual curves. A similar pattern of change in all variables occurred in both groups but with wide interindividual variation in the magnitude of response. Areas under the curve (arbitrary units) were expressed as median (range):

	LC	MC	P*
C-reactive protein	37 (31–46)	39 (32–46)	0·13
Interleukin 6	41 (37–45)	41 (38–43)	0·76
Albumin	90 (35–166)	71 (51–171)	0·44
Fibrinogen	70 (49–111)	69 (52–111)	0·70
FDPs	49 (69–130)	67 (35–119)	0·25
Cortisol	15 (7–34)	13 (7–30)	0·49
PMN elastase	37 (20–112)	46 (28–78)	0·59

*Mann–Whitney *U* test

In conclusion, a significant metabolic response occurs after both LC and MC. LC has no advantage over MC in reducing surgical trauma.

Inhibition of tumour necrosis factor activity by a synthetic retroviral peptide

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FG-10 is a synthetic peptide consisting of a ten amino acid sequence of the immunosuppressive retroviral transmembrane protein known as P15E. The deleterious clinical consequences of endotoxaemia are mediated via activation of neutrophils by tumour necrosis factor (TNF) in response to endotoxin (lipopolysaccharide; LPS). The aim, therefore, was to determine the effects of FG-10 on TNF production in response to LPS. The concentration of TNF in the supernatant of LPS-activated macrophages or neutrophils from healthy humans was measured by means of an enzyme-linked immunosorbent assay, with the following results:

	LPS alone	FG-10 alone	LPS plus FG-10
Macrophages	3052(356)	442(89)	2078(254)*
Neutrophils	1397(163)	433(105)	966(132)*

Values are mean(s.e.m.) expressed in pg ml^{-1} ($n = 5$). *$P < 0·05$ *versus* LPS alone (paired *t* test)

Thus FG-10 produced a slight but significant reduction in LPS-induced TNF production.

The effects of 10^{-6} mol l^{-1} FG-10 on expression of the activation marker CD11b and on hydrogen peroxide production by neutrophils in response to TNF were then examined using flow cytometry.

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	TNF alone	FG-10 alone	TNF plus FG-10
CD11b	1633(56)	1081(20)	1049(68)*
H_2O_2 production	36(0·5)	24·2(1·8)	16·8(0·5)†

Values are mean(standard error of difference) channel fluorescence ($n = 5$). *$P < 0{\cdot}05$; †$P < 0{\cdot}001$ *versus* TNF alone (paired t test)

Thus, although FG-10 inhibits TNF production only minimally in response to endotoxin, it prevents neutrophil activation in response to TNF. FG-10 may represent a potent therapeutic agent in prevention of the clinical effects of endotoxaemia.

Lipid peroxidation is increased rather than reduced in colorectal cancer

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The extent of tissue lipid peroxidation may affect the growth of normal and neoplastic cells. It has previously been shown that there is reduced lipid peroxidation in a variety of experimental cancers. Therapeutic manipulation that increases lipid peroxidation also results in reduced tumour growth. Conversely, some experimental cancers have reduced antioxidant systems, so conflicting with the above results. The extent of lipid peroxidation in human colorectal cancer, however, is not known.

Cancer tissue and distant normal mucosa were snap-frozen in liquid nitrogen immediately after surgery for colorectal cancer in 18 patients. Lipid peroxidation was assayed using the malonyldialdehyde (MDA) spectrophotometric method. Because lipid peroxides are derived from polyunsaturated fatty acids (PUFAs), these were measured together with saturated fatty acids (SFAs) by gas–liquid chromatography following separation of tissue phospholipid fractions.

The median (range) level of MDA in cancer tissue (1·0 (0·39–1·78) nmol per mg protein) was significantly increased compared with that from mucosa (0·79 (0·4–1·54) nmol per mg protein), $P = 0{\cdot}04$ (two-tailed Mann–Whitney U test). The level of PUFA was increased and that of SFA reduced in tumours compared with those in mucosa. There was an increase in the median (range) PUFA:SFA ratio in cancer tissue (0·78 (0·37–0·98)) compared with that in mucosa (0·61 (0·26–0·96)), $P = 0{\cdot}03$ (two-tailed Mann–Whitney U test).

Lipid peroxidation is increased in human colorectal cancer rather than reduced. In humans, agents that increase lipid peroxidation (such as dietary PUFAs) may be detrimental, while dietary antioxidants may be beneficial.

Macrophage failure in obstructive jaundice: association with intra-abdominal infection

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Obstructive jaundice predisposes to infection by endogenous Gram-negative bacteria, but the basis for this is unclear. The capacity of macrophages to respond to activation stimuli with the production of bactericidal nitric oxide and superoxide anion is critical for host defence against Gram-negative bacteria. The influence of 7-day obstructive jaundice on these parameters was assessed in 6-week-old Sprague–Dawley rats ($n = 40$) randomized to undergo bile duct ligation (BDL) or sham ligation (SL).

Peritoneal macrophage activation was assessed using colorimetric assays to measure superoxide anion generation in response to phorbol myristate acetate, and nitric oxide production following endotoxin stimulation. The mesenteric lymph node (MLN) complex was excised and cultured for Gram-negative bacteria using standard microbiological techniques.

	Superoxide (nmol per 90 min)	Nitric oxide (μmol)	MLN infection (%)*
BDL	0·02(0·01)†	0·23(0·05)†	75†
SL	0·55(0·23)	1·32(0·11)	0

Values are mean(s.e.m.). * Percentage of rats with infection of the MLN complex. †$P < 0{\cdot}05$ *versus* SL (Student's t test)

Bile duct ligation markedly impairs macrophage activation compared with sham ligation. This effect was associated with infection of MLNs with Gram-negative bacteria. These data suggest mechanisms that may underlie the susceptibility of jaundiced patients to Gram-negative infection.

Investigation of a novel pure antioestrogen using the Courtenay–Mills clonogenic assay

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Although classed as an antioestrogen in the treatment of breast cancer, tamoxifen exhibits intrinsic partial agonist activity, which may potentially reduce its clinical efficacy. Clinical studies are currently being undertaken with ICI 182780 (182), a novel pure antioestrogen. The antioestrogenic effects of 4-hydroxytamoxifen (Tam) and 182 on MCF 7 breast cancer cells have been investigated in the Courtenay–Mills clonogenic assay, which measures their ability to form anchorage-independent colonies in soft agar. This is expressed as a colony-forming efficiency (c.f.e.), determined by the percentage of cells that successfully form colonies with diameters > 60 μm.

The c.f.e. of the MCF 7 cells was significantly increased in the presence of 1 nmol l^{-1} oestradiol (E_2) compared with control conditions. This oestrogenic stimulation was inhibited by both 182 and Tam in a dose-dependent manner. However, at the typical pharmacological concentration of 1 μmol l^{-1}, 182 produced a significantly greater inhibition of colony formation than Tam ($P < 0{\cdot}001$, Student's t test).

	Control	E_2	E_2 plus Tam	E_2 plus 182
c.f.e. (%)	0·374	0·648	0·07	0·007

It is concluded that, *in vitro*, 182 produces more complete inhibition of the growth of oestrogen-responsive cells than Tam and may therefore offer potential therapeutic advantages in the treatment of advanced breast cancer.

Adjunctive intraoperative photodynamic therapy for colorectal cancer: reduced treatment time using a new photosensitizer

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Two disadvantages of clinical adjunctive intraoperative photodynamic therapy (PDT) using Photofrin are the long illumination time (15–20 min) and the need for a laser. The efficacy of intraoperative PDT has been compared using Photofrin and mTHPC, a new photosensitizer now becoming available for clinical use, in a mouse model of local recurrence.

COLO26 tumour was grown subcutaneously in the left hind leg of BALB/c mice. Animals were injected with equal doses of either photosensitizer 24 h before surgery. A standard surgical excision was performed so that all visible tumour was removed by an operator blind to both drug and light treatments. After surgery, tumour beds were illuminated where appropriate. The excised tumour weight was identical in all groups (0·57 g with 1·6 per cent coefficient of variation).

	Light		Palpable recurrence	
Drug	λ (nm)	Dose (J cm^{-2})	within 70 days	P*
mTHPC	652	2·5	5 of 20	<0·001
Photofrin	510	70·0	5 of 19	<0·001
None	—	—	17 of 20	—
mTHPC	—	—	9 of 10	0·70
Photofrin	—	—	9 of 10	0·81
None	652	2·5	8 of 10	0·76
None	510	70·0	9 of 10	0·71

* *Versus* surgery-only group (log rank test)

PDT using either Photofrin or mTHPC was equally effective in reducing local recurrence in this model. However, treatment time with mTHPC was only 25 s compared with 11 min for Photofrin. Use of this new photosensitizer greatly increases the practicality of adjunctive intraoperative PDT and opens up the possibility of replacing the laser with cheaper, less intense, light sources.

Pulmonary trapping of activated neutrophils following aneurysm repair

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Reperfusion of ischaemic tissue during aortic aneurysm repair generates thromboxane, activates neutrophils and leads to multiple organ dysfunction. The lung, however, is disproportionately damaged. This study examined the hypothesis that the more activated neutrophils leaving the ischaemic lower limbs are trapped by the lung.

Eighteen patients undergoing elective infrarenal abdominal aortic aneurysm repair had mixed venous and arterial blood samples taken simultaneously from a Swan–Ganz catheter and radial line respectively. Samples were obtained before, during and after aortic cross-clamping for estimation of neutrophil count, activity (flow cytometric estimation of free radical production) and thromboxane levels (radioimmunoassay)

The following results were obtained on aortic declamping:

		Neutrophil	
Blood sample	Thromboxane (pg ml^{-1})	Count ($\times 10^9$)	Activity (MFU)
Mixed venous	764(98)*	6·7(3·1)	174(31)*
Arterial	893(114)*	3·3(1·9)*†	91(22)*†

Values are mean(s.d.). MFU, mean fluorescence units. $P < 0{\cdot}01$ *versus* *preclamp and †mixed venous values (analysis of variance)

The data demonstrate an arterial–venous difference in neutrophil count and activity across the lung following aortic aneurysm repair. Pulmonary trapping of the more activated neutrophils may explain the disproportionate lung injury seen after aortic aneurysm repair.

Cardiopulmonary bypass impairs intestinal saccharide transport and increases gut permeability

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Gastrointestinal complications following cardiopulmonary bypass (CPB) carry a high mortality rate, occurring in 0·6–2 per cent of patients. The effects of non-pulsatile hypothermic CPB on intestinal absorption and permeability have been studied in 41 patients, employing oral 3-*O*-methyl-D-glucose, D-xylose, L-rhamnose and lactulose to assess active and passive carrier-mediated, transcellular and paracellular transport respectively. Patients were studied before, immediately after and 5 days after CPB.

Immediately after CPB there was a decrease in mean(s.d.) urinary excretion of 3-*O*-methyl-D-glucose (from 34·0(2·2) to 5·2(6·1) per cent, $P < 0{\cdot}0001$), D-xylose (from 25·4(1·4) to 4·1(0·8) per cent, $P < 0{\cdot}0001$) and L-rhamnose (from 8·3(0·6) to 2·6(0·4) per cent, $P < 0{\cdot}0001$). Permeation of 3-*O*-methyl-D-glucose and D-xylose returned to normal levels 5 days after CPB, while the level of L-rhamnose remained reduced at 6·6(0·5) per cent ($P < 0{\cdot}004$). Permeation of lactulose increased immediately after CPB (from 0·35(0·004) to 0·59(0·1) per cent, $P < 0{\cdot}02$), and the mean(s.d.) lactulose:L-rhamnose ratio increased (from 0·045(0·04) to 0·36(0·08), $P = 0{\cdot}004$), indicating a substantial rise in gut permeability.

In ten patients gastric mucosal blood flow was determined by laser Doppler flowmetry. A 48·7(7·0) per cent reduction in gastric mucosal laser Doppler flow was found 30 min after the institution of CPB ($P = 0{\cdot}0001$).

This study demonstrates reversible impairment of small bowel transcellular transport following CPB, which may be secondary to mucosal hypoperfusion. These findings have implications for the prevention of endotoxaemia following CPB, and for enteral and drug therapy in the perioperative period.

Effect of glucose intake on substrate utilization and energy expenditure in the surgical newborn infant

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Characteristics of carbohydrate metabolism in stable surgical newborn infants were determined from 21 metabolic studies on 11 infants. Each infant received 3 days of continuous total parenteral nutrition containing constant amounts of amino acids (2·5 g kg^{-1} day^{-1}) and fat (3·0 g kg day^{-1}) and different amounts of glucose (range 10–25 g kg^{-1} day^{-1}). Respiratory gas exchange and urinary nitrogen excretion were measured, enabling oxygen consumption, carbon dioxide production (V_{CO_2}), resting energy expenditure (REE) and the non-protein respiratory quotient (NPRQ) to be calculated. Glucose intake correlated with the following dependent variables:

NPRQ: $y = 0{\cdot}723 + 0{\cdot}015x$, $r = 0{\cdot}934$, $P < 0{\cdot}0001$
REE (kcal kg^{-1} day^{-1}): $y = 39{\cdot}45 + 0{\cdot}768x$, $r = 0{\cdot}650$, $P < 0{\cdot}005$
V_{CO_2} (ml kg^{-1} min^{-1}): $y = 3{\cdot}849 + 0{\cdot}183x$, $r = 0{\cdot}825$, $P < 0{\cdot}0001$
Respiratory rate: $y = 36{\cdot}93 + 0{\cdot}732x$, $r = 0{\cdot}460$, $P = 0{\cdot}06$

With glucose intake <18 g kg^{-1} day^{-1}, NPRQ was <1·0, indicating net fat oxidation. With glucose intake >18 g kg^{-1} day^{-1}, NPRQ was >1·0, indicating net glucose conversion to fat; there was an increase in the gradient of the correlation between the predictor variable of glucose intake and the dependent variables V_{CO_2} and REE. Thus, glucose intake is the principal determinant of glucose utilization and influences the metabolism of exogenous fat.

When glucose intake exceeds 18 g kg^{-1} day^{-1}: (1) net fat oxidation ceases and net fat synthesis occurs; (2) the thermogenic effect of glucose increases, implying a reduced efficiency of glucose metabolism; and (3) carbon dioxide production and respiratory rate increase.

Serotonin receptors in human jejunum

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Serotonin (5-hydroxytryptamine; 5-HT) is an important regulator of intestinal electrolyte transport in experimental animal studies. However, the physiological role of 5-HT in the regulation of human electrolyte transport is unclear. The aim of the present study was to examine the role of 5-HT in normal human transport by testing the hypothesis that 5-HT would stimulate chloride transport.

Segments of normal human jejunum were obtained from patients undergoing intestinal bypass for morbid obesity. Samples ($n = 5$; consecutive series, no exclusions) were mounted in flux chambers under short-circuit conditions. Chambers contained oxygenated Krebs' buffer at 37°C. 5-HT in different concentrations was added to separate flux chambers to test for concentration-dependent transport, the basic criterion of receptor-mediated action. Change in short-circuit current was recorded, because this is known to be a sensitive indicator of chloride transport (the main mode of action of 5-HT on electrolyte transport). During each experiment a control segment was examined histologically after haematoxylin and eosin staining.

	Short-circuit current (μA cm^{-2})		
	Basal	1 min	5 min
Control	30·6(27·0)	30·6(29·7)	30·8(31·1)*
5-HT (100 μmol l^{-1})	37·4(23·9)	48·0(28·9)	51·4(29·3)*
5-HT (1 μmol l^{-1})	30·5(16·4)	32·5(16·4)	37·8(18·8)

Values are mean(s.d.). *$P = 0{\cdot}13$ (paired t test)

The results show that 5-HT had no significant effect on short-circuit current in this preparation. This is an important negative finding, demonstrating for the first time that 5-HT may not stimulate chloride transport in humans.

Total body potassium is proportional to wound healing capacity in a malnourished subject

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Despite a recognized association, few studies have investigated the quantification of malnutrition and the measured change in local wound healing capacity.

Ten anorexic inpatients had lean body mass (potassium-40 whole-body detector measuring total body potassium (TBK)) and body-weight measured (after ethical approval). Wound healing was assessed by insertion of two subcutaneous 90-μm pore size, 10 cm × 1 mm polytetrafluoroethylene (PTFE) wound capillaries, which were extracted 5 and 10 days after insertion. Collagen accumulation was measured by hydroxyproline estimation during week 1 (malnourished) and the final week (renourished) of treatment. A hospital diet of 6·3 kJ increasing to 12·6 kJ after 7 days and 40–50 g protein provided over a mean of 48 (range 27–87) days was provided until normal weight for height was obtained. Two patients failed to complete the study.

Mean(s.d.) body-weight increased from 37·5(5·7) to 49·6(4·5) kg. Mean(s.d.) TBK increased from 1926(281) to 2292(289) mmol. The TBK increase during treatment was 343(242) mmol. The mean(s.d.) rate of collagen accumulation before treatment was 55·5(21) ng per cm PTFE per day and afterwards 91(30) ng per cm PTFE per day; the increase in collagen accumulation rate was 33·7(40·3) ng per cm PTFE per day. The correlation between the improved rate of collagen accumulation and improvement in TBK was 0·96 (Pearson's correlation coefficient, $P < 0·001$).

Despite interindividual variability in wound-healing capacity, these data indicate that the rate of collagen wound accumulation in the absence of local sepsis is directly improved with effective nutritional support.

Acute normovolaemic haemodilution in major abdominal surgery

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Acute normovolaemic haemodilution (ANH) involves venesection and isovolaemic replacement with colloid. The autologous blood is reinfused at the end of operation, thus conserving blood. Concerns include the safety of ANH in patients with arteriopathy and possible dilutional coagulopathy.

Forty-seven patients underwent ANH before abdominal aortic aneurysm (AAA; $n = 30$) or major bowel ($n = 17$) surgery. Eight patients with AAA had a history of myocardial infarction, five had angina and 26 had chronic obstructive airway disease. A mean (range) of 832 (726–939) ml blood was removed in the AAA group and 951 (866–1037) ml in the bowel surgery group to achieve target haematocrits of 0·30 and 0·28 respectively. Clotting studies (international normalized ratio (INR), activated partial thromboplastin ratio, fibrinogen level, activated clotting time (ACT)) were performed before and after ANH, and packed cell volume monitored during surgery. Bank blood was transfused at a trigger of 0·23–0·25. Nine of 30 patients with AAA and 11 of 17 in the bowel surgery group needed no homologous blood transfusion, despite a mean (range) operative blood loss of 1694 (1218–2169) ml and 1035 (667–1402) ml respectively. The mean (range) postdilution INR was prolonged from 1·0 to 1·3 (1·2–1·4) in the AAA group and from 1·0 to 1·4 (1·3–1·5) in the bowel surgery group, and was related to the volume of blood removed. The ACT was unaffected and no bleeding tendency was observed. There were no adverse clinical events related to ANH.

Provided normovolaemia is maintained, moderate haemodilution appears to be safe, even in patients with significant ischaemic heart disease. Although no bleeding tendency was seen, a preoperative clotting screen is advisable.

Metabolic response to operative stress in infants

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Energy metabolism and substrate utilization were studied in 19 infants before and after surgery. Anaesthesia was standardized, and operative stress score (OSS) and physical activity recorded. Energy and nitrogen intake were kept constant. Respiratory gas exchange was measured by indirect calorimetry before and after operation, continuously for the first 12 h and at 24 h, 48 h and 5 days. Urinary nitrogen excretion was measured. Resting energy expenditure (REE) and the non-protein respiratory quotient (NPRQ) were calculated.

Category	Baseline REE ($\text{kcal kg}^{-1}\text{ day}^{-1}$)	Peak REE ($\text{kcal kg}^{-1}\text{ day}^{-1}$)	P*
All infants	44·33(1·26)	51·21(2·03)	<0·001
OSS <7	47·50(2·80)	50·12(3·61)	0·18
OSS ≥7	43·20(1·32)	51·60(2·50)	<0·0001
Age <48 h	40·21(0·93)	45·84(2·07)	<0·05
Age ≥48 h	47·18(1·84)	59·29(3·04)	<0·005

Values are mean(s.e.m.). *Peak *versus* baseline REE

REE increased after operation, peaking at 2–4 h, and returned to baseline levels by 12–24 h. Peak REE was significantly higher than baseline REE ($P < 0·001$). REE increased significantly more after a major (OSS ≥7) than a minor (OSS <7) operation ($P < 0·05$). Among infants undergoing a major operation, REE increased significantly more in those ≥48 h old than in those <48 h old ($P < 0·05$). NPRQ did not change significantly, implying that substrate utilization was not altered by operation.

These data show that REE in infants increases after operation, that the size of the increase is related to the severity of the operation, and that the increase is greater in infants ≥48 h old.

Colonic mucosal replacement by seeded small intestinal stem cells

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Severe colonic mucosal disorders may require total colectomy, which has a significant morbidity rate. A novel method of colonic mucosal replacement by 'seeded' small intestinal stem cells (SISCs) has been developed.

In an inbred strain of rat (AO/OLA), a colonic loop was isolated with intact vascular pedicle and surgical mucosectomy performed. Epithelial fragments containing SISCs were isolated from the small intestine of postnatal animals by enzymatic disaggregation. Then 25 μl of the SISC suspension was seeded on to the denuded colonic muscle of six adult recipients. Six control animals had surgical mucosectomy without seeded SISCs. All colonic loops were retrieved after 14 days. Graft morphology was evaluated by histology and histochemistry.

Transplanted SISCs re-epithelialized the denuded colon in five of six recipients. The neomucosa had typical small intestinal morphology with well formed crypts and villi, as well as expression of alkaline phosphatase in the brush border. Control loops showed no evidence of epithelial regrowth, confirming total surgical mucosectomy.

In conclusion, SISCs have the capacity to interact with denuded colonic muscle, resulting in colonic re-epithelialization with neomucosa exhibiting a typical small intestinal phenotype. SISC transplantation may prove beneficial in disorders of colonic mucosa.

Defective cell-mediated immunity in long-term renal allograft recipients with skin cancer

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The increased incidence of squamous cell carcinoma (SCC) of the skin in recipients of renal allograft is now well recognized, with many of these patients developing multiple lesions.

The aim of this study was to compare cutaneous cell-mediated immunity (CMI) in patients with renal allografts and in controls. A standardized skin sensitivity kit, which introduces seven common antigens and one control substance intradermally, was applied to sun-exposed and non-exposed surfaces of each subject's forearm. Forty-eight subjects were studied: 11 recipients of renal allograft with a previous history of SCC, 23 allograft recipients with no such history, matched for duration of immunosuppression, and 14 healthy controls, matched for age, sex and skin type. Reactions to the antigens (diameter of induration) were assessed by two observers after 48 h:

	Sun-exposed skin		Non-exposed skin	
Subject	Negative	Sum	Negative	Sum
SCC with allograft	9 of 11	0·5	10 of 11	0·3
Control allograft	13 of 23	1·4	17 of 23	1·2
Normal controls	0 of 14	15	2 of 14	13·0

Negative, patients with no reaction to any of the antigens; Sum, mean sum of diameters of induration

Recipients of long-term renal allograft have significantly depressed CMI compared with controls ($P < 0{\cdot}001$, χ^2 test). In addition, this study indicates that the CMI is further reduced in patients who have developed cancer.

T lymphocyte activation and inhibition of tumour growth with the superantigen staphylococcal enterotoxin B

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Staphylococcal enterotoxin B (SEB) selectively activates certain T cell subsets. It represents an alternative to anti-CD3 monoclonal antibody, which is used for T lymphocyte activation *in vitro* but is unsuitable for *in vivo* use because it can also cause immunosuppression. The ability of SEB to activate T lymphocytes *in vivo* and to reduce tumour growth was investigated in an established tumour model.

C3H mice received 50 mg SEB (treatment group) or 0·5 ml phosphate-buffered saline (PBS) (control group) intraperitoneally. At 18 h mice were killed and splenocytes extracted and cultured with 100 units ml^{-1} interleukin (IL) 2 (treatment and control groups) or IL-2 plus 0·5 μg ml^{-1} anti-CD3 (control group only). On day 5 a 4-h chromium-release assay was used to assess the ability of cultured cells to lyse the tumour target CL62 cells.

	Lytic units
Control (IL-2 only)	0
Control (IL-2 plus anti-CD3)	1·1(0·5)
Treatment (IL-2)	4·6(1·0)*

Values are mean(s.d.). *$P < 0{\cdot}05$ *versus* both control groups (Student's *t* test)

Twenty C3H mice received 2 × 10^5 CL62 cells intravenously. On day 4, group 1 ($n = 10$) received 0·5 ml PBS and group 2 ($n = 10$) 50 mg SEB intraperitoneally. At day 14, mice were killed and lung metastases counted.

Group	No. of metastases
1 (tumour plus PBS)	229(22)
2 (tumour plus SEB)	136(23)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ (Student's *t* test)

SEB activates T lymphocytes *in vivo* and reduces tumour growth in an established lung metastasis model.

Orthotopic transposition following small bowel transplantation in rats corrects overgrowth of potentially pathogenic bacteria

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An overgrowth of pathogenic organisms occurs following rat heterotopic small bowel transplantation (HSBT). This study assessed whether the bacterial microflora return to normal after delayed orthotopic transposition of the graft (OSBT), a procedure used in clinical practice.

HSBT was performed in DA rats. Before transplantation, graft lumens were flushed with 20 ml 0·05 per cent chlorhexidine solution. The ends of the graft were exteriorized as stomas. All animals received 1 mg gentamicin subcutaneously during operation. OSBT was performed at 14 days, following resection of a 15-cm mid-intestinal loop of host gut.

Small bowel was sampled as follows ($n = 6$–8 per group): group 1, controls (no transplantation); group 2, HSBT, host on day 14; group 3, HSBT, graft on day 14; group 4, OSBT, graft on day 28. Colonies were counted and identified. Gut effluent was cultured and bacterial colonies identified and counted.

	Group 1	Group 2	Group 3	Group 4
Median bacterial count ($\times 10^6$)	112	170	724*	363

*$P < 0{\cdot}01$ *versus* host gut (group 2) (Wilcoxon rank sum test on log$_{10}$ [bacteria per gram dry weight of bowel])

An overgrowth of *Staphylococcus epidermidis* was apparent in the heterotopic grafts at 14 days. This was reversed following orthotopic transposition, with a return to a more normal bacterial profile.

These findings suggest that early interposition of a small bowel transplant into an orthotopic position may prevent an alteration in the small bowel ecology towards potentially pathogenic organisms capable of translocation.

Immunomodulation of cryopreserved pancreatic islets by γ-irradiation

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Cryopreservation is an integral part of human islet transplant programmes. Before islet transplantation can be offered to patients with juvenile diabetes it is necessary to reduce islet immunogenicity (immunomodulation). It has previously been shown that immunomodulation of rat islets by γ-irradiation (2·5 Gy) before transplantation across a strong allograft barrier leads to long-term graft acceptance. Cryopreservation and γ-irradiation have not previously been combined. The purpose of this study was therefore to investigate the effect of combined cryopreservation and γ-irradiation on rat islet viability.

Purified rat islets were γ-irradiated (2·5, 5·0, 10·0, 15·0 or 20·0 Gy), either before or after cryopreservation. After tissue culture, islet recovery was measured and viability assayed by glucose-stimulated insulin release in a perifusion system. Median numerical loss was significantly greater after the irradiation–cryopreservation than after the cryopreservation–irradiation protocol (49 *versus* 31 per cent, $P < 0{\cdot}05$). The median insulin release from islets after the irradiation–cryopreservation protocol was zero, whereas release after cryopreservation–irradiation was no different from that from control cultured islets.

In conclusion, γ-irradiated islets cannot be cryopreserved successfully, whereas cryopreserved islets can be γ-irradiated. The latter sequence should therefore be used for immunomodulation of cryopreserved islets.

Natural killer cell depression following surgery: changing cell numbers and changing function

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Depression of natural killer (NK) cell function following surgery for colorectal cancer may be important in allowing micrometastases to become established. It is unclear whether postoperative suppression of NK activity is the result of a decrease in NK cell cytotoxicity or simply a reduction in cell numbers.

In an attempt to answer this question, both the absolute number of NK cells (CD16) and their lytic ability against a K562 target were measured before operation and on days 1, 3 and 7 after surgery in 35 patients who underwent elective, potentially curative, resection for colorectal cancer. NK cells were identified by flow cytometry using the monoclonal antibody Leu11c against the CD16 cell surface marker, and percentage lysis calculated from a standard chromium-release assay at an effector:target ratio of 2·5 CD16 cells:1.

	Before operation	Day 1	Day 3	Day 7
CD16 count ($\times 10^9$ l^{-1})	0·21 (0·12–0·28)	0·16 (0·12–0·23)	0·13 (0·08–0·22)*	0·17 (0·09–0·25)
CD16 lysis (%)	25·5 (21·0–34·0)	18·0 (13·0–21·0)*	23·0 (16·3–35·1)	24·8 (21·0–31·0)

Values are median (interquartile range) $^*P < 0·05$ *versus* before operation

The postoperative decrease in NK cell function is caused by a reduction in both NK cell numbers and lytic activity. Adjuvant immunotherapy should perhaps aim to increase the cytotoxicity of NK cells.

Prevalence of congenital hypertrophy of the retinal pigment epithelium in familial colorectal cancer

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Congenital hypertrophy of the retinal pigment epithelium (CHRPE) and mandibular osteoma have been identified and used to assess risk in families with familial adenomatous polyposis (FAP). Less is known of their incidence in non-polyposis familial colorectal cancer. CHRPE and mandibular osteoma were looked for in three groups without FAP: (1) individuals with colorectal cancer and a first-degree family history of colorectal cancer (FH positive); (2) individuals with sporadic colorectal cancer (FH negative); and (3) control subjects with no personal or family history of colorectal cancer.

All individuals underwent ophthalmoscopy and orthopantography. The ophthalmologist and radiologist were unaware of the individual's group.

	Patients with colorectal cancer		
	FH positive ($n = 22$)	FH negative ($n = 28$)	Controls ($n = 21$)
CHRPE absent	10 (45)	27 (96)	21
CHRPE <4	7 (32)	1 (4)	0
Multiple CHRPE	5 (23)	0	0

Values in parentheses are percentages

No individual had mandibular osteoma. The degree of CHRPE did not correlate with the extent of the family history. The frequency of multiple CHRPE in patients with a family history suggests that it may be a marker of a constitutional genetic defect. Relatives of such patients may be at particular risk of colorectal cancer, and the phenotypic marker may be of value in the assessment of risk.

Colitis in the cottontop tamarin: a model of ulcerative colitis

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A satisfactory animal model of ulcerative colitis has not been demonstrated, and in colitis research emphasis has been directed towards the study of experimentally induced colonic inflammation in rodents. The cottontop tamarin suffers from a spontaneous form of inflammatory bowel disease that shows many similarities to human ulcerative colitis. Examination of 40 animals, by endoscopy and rectal biopsy, has demonstrated this to be a continuous disease, with diffuse mucosal inflammation, cryptitis and crypt abscesses. The pathology is similar to that seen in human ulcerative colitis. Histochemical studies have demonstrated an increase in sialomucin and a reduction in sulphomucin levels during disease activity. The colitis responds to therapy with olsalazine and prednisolone.

Colitis in the cottontop tamarin is unique in being complicated by multiple, flat, right-sided colonic carcinoma. In addition, there is development of liver disease resembling sclerosing cholangitis.

Spontaneous colitis in the cottontop tamarin demonstrates many similarities to human ulcerative colitis and so represents the first real animal model. Further studies should permit a greater understanding of the mechanism of action of inflammatory mediators, and allow the assessment of novel therapeutic regimens.

Identification of mutant p53 in the stool of patients with colorectal cancer

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Faecal occult blood tests have been extensively evaluated in screening for colorectal cancer. The most widely used test, Haemoccult (Rohm Pharma), has a sensitivity for colorectal cancer of 50–70 per cent. Tumour-derived mutations and suppressor genes potentially provide more specific markers. As p53 is mutated in more than 75 per cent of colorectal cancers, and as most of these mutations lead to a common conformational change in the p53 protein, certain antibodies can detect most mutant forms of p53.

In this study, an enzyme-linked immunosorbent assay (ELISA), based on the monoclonal antibody 240 which recognizes mutant p53, has been used to screen a panel of stool taken from patients with colorectal cancer and normal age-matched controls. Control subjects had colonoscopy and/or double-contrast barium enema as investigation of positive Haemoccult tests or iron-deficiency anaemia. None had colorectal neoplasia.

Fourteen of 18 of the samples from patients with cancer were positive, with a range of 0·25–1·85 ng ml^{-1} p53, while seven of 26 of the normal samples also gave a positive result. The range of p53 detected in the normals was 0·4–1·0 ng ml^{-1}. Four of the seven normal patients had iron-deficiency anaemia for which no cause was found. The overall sensitivity of the p53 ELISA for carcinoma was 77 per cent, which compares favourably with that of 3-day Haemoccult testing and warrants further evaluation.

D-dimer as a predictor of tumour stage in the surgery of colorectal cancer

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Anticoagulant therapy may reduce tumour metastases and prolong survival. While tumours are known to cause hypercoagulability, there is no convenient method for quantifying the level of haemostatic disturbance. The aim of this study was to examine a new range of biochemical markers for clinical thromboembolic disease so as to determine their relationship to the stage of malignant disease.

A group of patients admitted for resection of colorectal malignancy was compared with patients undergoing laparotomy for benign disease (elective open cholecystectomy). Blood samples were taken by clean venepuncture the day before operation. The markers used were antithrombin (AT) III activity, AT-III level and cross-linked fibrin degradation product (D-dimer) level.

	AT-III activity (%)	AT-III concentration (μg ml^{-1})	D-dimer concentration (μg ml^{-1})
Benign ($n = 12$)	106·2(3·2)	358·6(10·0)	70·3(12·9)
Malignant ($n = 12$)	100·3(5·2)*	326·6(19·8)*	670·8(347·9)†

Values are mean(s.e.m.). **P* not significant; †$P < 0·05$

There was no significant difference in AT-III activity or concentration between the two groups. D-dimer level was significantly higher in the malignant group. There were no Dukes' A tumours; five (42 per cent) Dukes' B and seven (58 per cent) Dukes' C. The normal range of D-dimer concentration was 30–160 μg ml^{-1} (i.e. mean(2 s.d.)). All patients with Dukes' C tumours and only one with a Dukes' B cancer had levels >160 μg ml^{-1} ($P = 0·006$, Fisher's exact test).

The preoperative D-dimer level is a useful predictor of tumour stage, and may facilitate the selection of patients for high-dose anticoagulant therapy to reduce metastases.

Safety of dietary restriction retesting in Haemoccult screening for colorectal cancer

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Certain foods can cause false-positive results when using guaiac-based faecal occult blood tests. In trials of Haemoccult (Rohm Pharma) screening for colorectal cancer, dietary restriction retesting is used to minimize the number of subjects undergoing unnecessary colonoscopy. All subjects submitting positive tests are requested to repeat the tests with appropriate dietary restriction. Because colorectal neoplasms bleed intermittently, a delayed retest 3 months later is sent to those with a negative first retest. Only those in whom a retest is positive are offered further investigation.

The aim was to investigate the safety of this policy by following up patients who did not undergo colonoscopy because their retests were negative or not performed.

From April 1986 to May 1990, 35 260 subjects have undertaken 52 354 rounds of screening at 2-yearly intervals, and all have been followed for a minimum of 27 months. The initial test was positive on 1290 occasions (2·5 per cent); 566 (44 per cent of initial positives) remained positive, investigation revealing 94 (48 per cent Dukes' stage A) cancers. Thirteen cancers (two stage A) have subsequently presented among the 724 subjects whose tests 'became' negative. This interval rate (18·0 per 1000 screens) is significantly higher than that following an initial negative test (1·4 per 1000) ($P < 0{\cdot}001$).

Although this policy reduces screening costs (by reducing the number of colonoscopies performed) it cannot be recommended because of the high risk of colorectal cancer in subjects with an initial positive test result.

Germ-line mutations in the adenomatous polyposis (*APC*) gene

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The recent identification of the adenomatous polyposis (*APC*) gene has enabled mutational analysis of patients with familial adenomatous polyposis (FAP) and accurate presymptomatic diagnosis in their at-risk relatives.

In this study the technique of denaturing gradient gel electrophoresis (DGGE) has been applied in mutational analysis. The 15 exons of the *APC* gene have been divided into 37 regions for analysis; 21 of these have been studied.

The patients comprised 19 index cases with FAP and one case of apparently sporadic colonic adenomatous polyps. Eleven DGGE variants have been identified in the patients with FAP. Four of these occurred in region 'e' of exon 15 and one, a 5-base pair deletion in exon 15g, was seen in two unrelated index cases.

The one sporadic case (in a patient aged 61 years) had congenital hypertrophy of the retinal pigment epithelium, a phenotypic feature of FAP. There was, however, no family history of colorectal cancer, and the patient has as yet developed only two polyps. Mutational analysis identified a DGGE variant in exon 15.

This study has shown DGGE to be a highly effective method of mutational analysis and suggests that there are mutation hot-spots in the *APC* gene. The identification of a DGGE variant in a patient with non-FAP polyps suggests a wider role for the *APC* gene in identifying genetic predisposition to colorectal neoplasia.

Detection of occult colorectal liver metastases

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In a previous study the authors have shown that overt liver metastases can be detected by direct measurement of associated changes in liver blood flow, using duplex colour Doppler sonography (DCDS).

In this study, the use of DCDS was assessed in the early detection of occult colorectal liver metastases.

Hepatic arterial and portal venous blood flows were measured in 40 healthy volunteers and 130 patients with colorectal cancer, 63 with overt liver metastases and 67 with an apparently disease-free liver on the basis of findings at computed tomography (CT) and laparotomy.

There was a clear separation of the Doppler perfusion index values (DPI: ratio of hepatic arterial to total liver blood flow) in patients with overt liver metastases compared with those in controls (mean(s.d.) 0·49(0·12) *versus* 0·14(0·06) respectively, $P < 0{\cdot}0001$). Of the 67 patients with an apparently disease-free liver, 37 also had an abnormally raised DPI at the time of laparotomy. After 1 year of follow-up, 17 had developed liver metastases and seven had died. The remaining 30 patients with normal DPIs remain disease-free.

The data suggest that DCDS measurement of DPI is more sensitive than CT and is therefore of value in the early detection of occult colorectal liver metastases.

Ventilatory changes during laparoscopic and open cholecystectomy: a randomized trial

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It has been suggested that arterial carbon dioxide levels may rise considerably during laparoscopic cholecystectomy. The accuracy of measurement of end-tidal carbon dioxide levels in this situation is unclear.

As part of a randomized study, ventilation requirements, arterial blood gas levels and end-tidal carbon dioxide have been assessed at the beginning of surgery and at the time of gallbladder removal during open cholecystectomy (control group, $n = 30$) and laparoscopic cholecystectomy ($n = 30$). Groups were well matched for preoperative demographic data and pulmonary function. There was no significant difference between the two groups in ventilation requirements, arterial carbon dioxide tension (P_{aCO_2}) and end-tidal carbon dioxide tension (P_{etCO_2}) at the beginning of surgery. Mean(s.d.) values at the time of gallbladder removal were:

	Open	Laparoscopic	P*
Ventilation minute volume (l min^{-1})	5·2(1·0)	6·2(1·1)	0·0012
Peak airway pressure (cmH$_2$O)	18(4)	23(4)	<0·0001
P_{etCO_2} (kPa)	4·7(0·4)	5·4(0·8)	0·0003
P_{aCO_2} (kPa)	5·5(0·7)	6·1(1·3)	0·037
P_{a-etCO_2} difference (kPa)	0·78(0·54)	0·70(0·73)	0·62

*Student's *t* test

In response to a rise in P_{etCO_2}, ventilation was increased significantly in the laparoscopic group, but P_{etCO_2} and P_{aCO_2} still remained significantly raised. Peak airway pressure was also significantly higher in the laparoscopic group. The 95 per cent limits of agreement between P_{etCO_2} and P_{aCO_2} were poor in both groups ($-0{\cdot}4$ to $+1{\cdot}7$ kPa).

In conclusion, carbon dioxide insufflation during laparoscopic cholecystectomy results in a significant but variable rise in P_{aCO_2}. Measurement of end-tidal carbon dioxide has poor precision in monitoring this rise. It is suggested, therefore, that patients with respiratory disease undergoing laparoscopic cholecystectomy have intraoperative arterial blood gas monitoring.

Dacarbazine and interferon confer no benefit in stage I malignant melanoma

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The results of a prospective randomized trial of adjuvant therapy in high-risk non-metastatic malignant melanoma are reported. Twenty-six patients with stage I malignant melanoma of thickness >1·5 mm or Clark level 3 were randomized to receive either adjuvant treatment (dacarbazine (DTIC) and interferon; $n = 14$) or observation ($n = 12$). Ethical approval was obtained. The mean age for men ($n = 8$) was

45·0 years and for women ($n = 18$) 48·3 years. Mean thickness in the treatment group was 2·9 (range 0·8–7·0) mm compared with 2·6 (range 0·8–5·0) mm in the observation group. Immunotherapy with DTIC and interferon was given in cycles; all patients completed the treatment schedule.

At 5 years, six deaths had occurred in the treatment group and two in the observation group ($P < 0·5$, 95 per cent confidence interval 0·6–10·4). Metastatic melanoma was confirmed in all eight patients who died. Mean thickness in the patients who died was 3·8 mm. Statistical analysis identified the relative risk of mortality to be 2·6 times greater in the treatment than in the observation group. In view of these results, randomization was suspended.

In conclusion, adjuvant treatment with DTIC and interferon in high-risk stage I malignant melanoma confers no benefit and is associated with an unacceptable mortality rate.

Mechanism of action of parathyroid hormone-related protein in hypercalcaemia

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In animals, parathyroid hormone-related protein (PTHrP) is said to cause hypercalcaemia by increasing the level of renal tubular adenosine 3′,5′-cyclic monophosphate (UcAMP), thus stimulating the renal tubular reabsorption of calcium (RTRCa) via the kidney.

The aim of this study was to determine whether similar effects of PTHrP on the renal tubule could be detected in patients with humoral hypercalcaemia of malignancy (HHM). Seventeen patients with primary hyperparathyroidism were used as controls. Plasma and urine were collected from a consecutive series of 60 patients with hypercalcaemia.

Thirty of 43 patients with malignant disease were shown to have a raised PTHrP level, and two had an elevated parathyroid hormone (PTH) level. UcAMP and RTRCa were measured in all patients. PTHrP levels correlated with UcAMP in patients with malignancy ($r_S = 0·37$, $P < 0·05$). UcAMP was significantly higher in patients with raised PTHrP and HHM (see *Table*), with shift of the calcium excretion curve to the right indicating an increase in RTRCa.

	Serum calcium (mmol l^{-1})	UcAMP/GFR (nmol l^{-1})	Calcium excretion (mmol l^{-1})
Benign			
PTH positive	2·87(0·09)	237·6(68·4)	117·5(27·9)
Malignant			
PTHrP negative	3·2(0·2)	64·2(12·7)	204·4(82·7)
PTHrP positive	3·5(0·1)	290·8(101·0)*	122·4(18·9)

Values are mean(s.e.m.). GFR, glomerular filtration rate. *$P < 0·05$ (Mann–Whitney U test)

It is concluded that PTHrP is humorally secreted by malignant tumours and its marked renal effects are important mediators of HHM.

5-Aminosalicylic acid increases colonic mucosal oxidation of glucose

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5-Aminosalicylic acid (5-ASA)-type drugs are thought to reduce inflammation by blocking prostaglandin production and scavenging free radicals. Alternatively, 5-ASA may increase mucosal oxidation of energy substrates essential for maintenance of cellular activity. Three biopsies (3–12 mg wet weight) from five resected sigmoid colons were incubated in cell culture medium containing 20 mmol l^{-1} 5-ASA with [^{14}C]glucose, [^{14}C]glutamine or [^{14}C]butyrate. Paired controls were incubated in medium containing normal saline instead of 5-ASA. The evolved [^{14}C]carbon dioxide was captured and quantified by liquid scintillation counting and the substrate flux calculated. Lowry protein estimations of the biopsies were performed.

	Normal saline*	5-ASA*	t
Glucose	6·0(1·5)	10·7(3·1)	2·89†
Glutamine	15·3(1·6)	19·2(2·1)	1·73‡
Butyrate	377·0(74·7)	294·5(44·5)	1·99‡

*Values are mean(s.e.m.) expressed as pmol substrate oxidized per μg protein per h. †$P = 0·044$; ‡$P > 0·05$

5-ASA significantly increases the oxidation of glucose in normal colonic mucosa. It has no effect on the β-oxidation of butyrate, the major fuel source for colonic mucosa. This facilitation of glucose oxidation may, by an unknown mechanism, result in additional energy to maintain and repair damaged mucosa in inflammatory bowel disease.

Low molecular weight heparin inhibits intimal proliferation in cultured human saphenous vein

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Smooth muscle cell (SMC) culture and *in vivo* animal studies have shown that heparin can inhibit the development of intimal hyperplasia. In this dose-ranging study, the effect of low molecular weight heparin (LMWH) on intimal proliferation in cultured human saphenous vein was investigated.

Thirty paired segments of saphenous vein were opened longitudinally, pinned out and incubated at 37°C for 14 days in culture medium with 30 per cent fetal calf serum. LMWH was added to the medium of one of the paired segments at 1, 10 and 100 μg ml^{-1} (five veins for each dose). 5-Bromo-2′-deoxyuridine (BrdU) was used to label all proliferating cells during the final 96 h of the culture period. Neointimal thickness was measured by two independent observers.

	LMWH concentration (μg ml^{-1})		
	1	10	100
Mean neointimal thickness (μm)			
Control	26	17	20*
LMWH	21	13	9
BrdU-labelled cells (%)			
Control	25	29	30†
LMWH	24	22	13

95 per cent confidence interval for difference between means *6·2–17 and †0·5–33 (paired t test)

The results show that in this model of human vein graft intimal hyperplasia, high-dose LMWH inhibits SMC proliferation and prevents intimal thickening.

Effect of the superantigen toxic shock syndrome toxin *in vivo*

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Toxic shock syndrome is a clinically defined entity observed following the use of tampons, surgical packs or prostheses. Cardiovascular collapse follows activation of a specific set of T lymphocytes by the superantigen toxic shock syndrome toxin (TSST) 1, which binds exclusively to the Vβ_2 chain of the T cell receptor. Animal models of the syndrome suggest that lifelong immune damage follows such activation.

Twelve survivors of the syndrome were investigated longitudinally using an antibody developed to the Vβ_2 chain. Significant changes were observed in the composition of the circulating lymphocyte populations. Proliferation assays demonstrated that patients' lymphocytes responded to recall antigens, TSST-1 and an antibody to Vβ_2 in all phases of recovery.

The *Table* shows cell typing data:

Time after first symptom (weeks)	$V\beta_2$-positive cells as percentage of total T cells	Percentage of $V\beta_2$-positive and CD4-positive cells	Percentage of $V\beta_2$-positive and CD45RA-positive cells
2	15(2)	2(1)	5(2)
4	10(3)	30(4)	42(3)
6	8(3)	48(4)	53(5)
Normals	9(3)	49(5)	50(5)

Values are mean(s.e.m.)

Superantigen *in vivo* therefore leads to acute distortion of the $V\beta_2$ T lymphocyte subset. Provided the patient survives the initial illness, there are no long-lasting immunological sequelae.

Immunological basis for vein graft stenosis

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The aetiology of vein graft stenosis is poorly understood.

Vein samples of proximal and distal prebypass long saphenous vein were taken from 88 patients undergoing distal bypass. Paraffin sections were stained with antibodies to smooth muscle cells (SMCs – desmin and actin), macrophages (Mac387), endothelial cells (JC70 and von Willebrand's factor) and leucocytes (CD68, CD45, CD20, CD45RO). Frozen sections were stained for lipid. The patients were then entered into a graft surveillance programme using colour duplex ultrasonography and intra-arterial digital subtraction angiography to identify graft stenosis.

Eleven patients developed stenosis.

	No stenosis ($n = 77$)	Stenosis ($n = 11$)	P*
Macrophages	9	9	<0·001
Lymphocytes	30	9	<0·025
Subendothelial SMCs	50	11	<0·05
Lipid	0	0	

* χ^2 test with Yates' correction

There was no association between the degree of endothelial cell loss and the development of stenosis.

The presence of macrophages and lymphocytes in the vein wall before bypass increases the likelihood of vein graft stenosis. This adds further support to the hypothesis that vein graft stenosis occurs due to pre-existing abnormality in the vein.

Psychological factors in non-specific abdominal pain

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The hypothesis that non-specific abdominal pain (NSAP) may have a detectable psychological component that might be used to predict outcome was tested. A total of 131 patients aged 14–40 years, admitted with acute abdominal pain, were assessed using the General Health Questionnaire (GHQ), the Hospital Anxiety and Depression (HAD) questionnaire and a structured interview.

Of 61 patients with NSAP, more had a psychosocial problem identified by the admitting registrar ($\chi^2 = 7{\cdot}28$, 1 d.f., $P < 0{\cdot}01$) and marginally more had high questionnaire scores. The risk of having NSAP was high when an abnormality on interview accompanied high questionnaire scores (relative risk 1·93 (95 per cent confidence interval (c.i.) 1·35–2·77)) and when prodromal pain had lasted >7 days (relative risk 2·13 (95 per cent c.i. 1·55–2·92)). After 2 years, patients with continuing pain had higher HAD ($\chi^2 = 6{\cdot}57$, 1 d.f., $P < 0{\cdot}02$) and Spielberger anxiety trait ($\chi^2 = 6{\cdot}50$, 1 d.f., $P < 0{\cdot}02$) scores; NSAP was associated with persisting pain (relative risk 2·22 (95 per cent c.i. 1·10–4·48)).

Psychosocial factors are implicated in NSAP and in chronic pain, but the sensitivity and specificity of questionnaire assessment are too low to be useful in diagnosis.

Perioperative renal tubular dysfunction in patients with obstructive jaundice: value of urinary enzymological studies

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Surgical intervention in obstructive jaundice is associated with a significant mortality rate, attributed largely to the development of acute renal impairment, which may be underdiagnosed using serum creatinine measurements.

The urinary activities of the proximal tubular brush border enzymes γ-glutamyl transpeptidase (GGT) and alanine aminopeptidase (ALAP), and the lysosomal hydrolase *N*-acetyl-β-D-glucosaminidase (NAG) were measured in 14 patients with jaundice (group 2), in 45 undergoing laparotomy (group 1) and in 20 having aortic reconstructive surgery (group 3).

Surgical intervention in group 1 had little effect on the urinary activities of NAG, GGT and ALAP (24(16) before *versus* 30(28) after surgery, 3·8(1·3) *versus* 4·1(3·8) and 1·1(0·7) *versus* 1·3(1·2) units per mmol creatinine respectively). In the jaundiced patients (group 2) both preoperative and postoperative levels were significantly raised: NAG 236(153) *versus* 328(182), $P < 0{\cdot}01$; GGT 6·6(2·5) *versus* 11·5(5·0), $P < 0{\cdot}05$; and ALAP 5·8(4·1) *versus* 10·1(6·1), $P < 0{\cdot}01$. No correlation existed between the duration or degree of hyperbilirubinaemia and the detected enzymuria. Urinary NAG activity was raised following aortic surgery (45(38) *versus* 128(98) units per mmol creatinine, $P < 0{\cdot}05$), although less significantly than in the jaundiced group. The serum creatinine level before and after surgery remained static in the jaundiced (92(32) *versus* 89(20) μmol l^{-1}) and aortic (92(49) *versus* 90(47) μmol l^{-1}) groups.

Urinary enzymology highlights proximal tubular damage in patients with obstructive jaundice, augmented by surgical intervention. Serum creatinine measurements which lack this sensitivity are of limited value.

Monocyte production of tumour necrosis factor in acute pancreatitis is related to outcome

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Excessive production of tumour necrosis factor (TNF) α is widely believed to be responsible for many of the features of septic shock, but its role in the pathophysiology of the systemic effects of acute pancreatitis remains controversial. In an attempt to overcome the limitations of plasma TNF measurement a study was made of the capacity of isolated monocytes from 11 patients with acute pancreatitis to produce TNF *in vitro*.

There was a strong positive correlation between the acute physiology score and lipopolysaccharide-induced TNF production on the first day after admission ($r = 0{\cdot}81$, $P < 0{\cdot}01$). Stimulated TNF production was significantly higher in patients with a complicated or fatal outcome ($n = 6$; median TNF 18·6 (range 10·8–56) ng per 10^6 cells) than in those with an uncomplicated course ($n = 5$; median TNF 4·8 (range 4–10·8) pg per 10^6 cells) ($P = 0{\cdot}01$).

These results lend support to the hypothesis that excessive TNF production by monocytes and macrophages plays a role in the pathophysiology of the systemic effects of acute pancreatitis.

Effect of splenectomy on lymphocyte subsets in patients undergoing radical resection for gastric cancer

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The authors have previously shown that splenectomy, as part of potentially curative resection for gastric cancer, is associated with significantly higher operative mortality and morbidity rates than potentially curative resection without splenectomy. They wondered whether this was due, in part, to an effect of splenectomy on immune function.

To test this hypothesis, changes in the lymphocyte subsets of patients who underwent either radical gastrectomy alone ($n = 16$) or gastrectomy plus splenectomy ($n = 10$) were measured. The levels of

T lymphocytes (CD3), T helper cells (CD4) and T suppressor-cytotoxic cells (CD8) were measured by means of monoclonal antibodies, before operation and on days 2, 7 and 14 afterwards.

	Before operation	Day 2	Day 7	Day 14
Gastrectomy alone				
CD3	1·28	0·77	0·82	0·87
CD4	0·80	0·41	0·55	0·61
CD8	0·60	0·37	0·38	0·35
CD4:CD8	1·14	1·16	1·57	1·50
Gastrectomy plus splenectomy				
CD3	1·30	0·86	0·67	0·10
CD4	1·02	0·46	0·66	0·96
CD8	0·49	0·27	0·15*	0·37
CD4:CD8	1·95	2·20	3·60†	3·06

Values are median cell count ($\times 10^9 l^{-1}$). *$P = 0·01$; †$P < 0·01$ *versus* gastrectomy alone

A significant reduction in CD8 cell count and a prolonged increase in the CD4:CD8 ratio were found after operation in patients who underwent splenectomy. Such changes in immune function may increase morbidity and mortality rates after resection for gastric cancer. Their long-term impact on survival also merits study.

Effect of portal pressure on pancreatic blood flow in normal cats and those with chronic pancreatitis

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Clinically, portal pressure is raised in alcoholic chronic pancreatitis. Previously, the authors have shown that pancreatic blood flow is reduced in cats with chronic pancreatitis. In the present study the effect of portal hypertension on pancreatic blood flow in cats was studied.

Pancreatic blood flow was measured by a hydrogen gas clearance technique. Portal pressure was measured through a portal vein catheter. In eight cats with chronic pancreatitis (created by narrowing the main pancreatic duct 5 weeks beforehand) and eight control animals, portal pressure was increased in increments up to 24 mmHg by inflating a cuff around the portal vein. Pancreatic blood flow was measured at each increment of portal pressure.

Normal mean(s.e.m.) basal portal pressure was 8·0(0·3) mmHg compared with 8·4(0·6) mmHg in chronic pancreatitis (P not significant). Normal mean(s.e.m.) basal vascular resistance was 1·6(0·1) *versus* 2·6(0·2) mmHg per ml per min per 100 g pancreas in pancreatitis ($P < 0·05$, Mann–Whitney U test).

	Portal pressure (mmHg)					
Group	Basal	12	15	18	21	24
Control blood flow*	61(5)	60(8)	60(8)	48(9)	46(11)	31(7)‡
Slope (blood flow/portal pressure)	−0·2 ($r = 0·9$)			−3§ ($r = 0·9$)		
Pancreatitis blood flow*	49(5)†	36(6)†	29(5)†‡	28(4)†‡	22(6)†‡	13(4)†‡
Slope (blood flow/portal pressure)	−2 ($r = 0·9$)			−2 ($r = 0·9$)		

*Values are mean(s.e.m.). †$P < 0·05$ *versus* controls (Mann–Whitney U test). ‡$P < 0·05$ *versus* basal pressure; §$P < 0·05$ *versus* slope from basal to portal pressure of 15 mmHg (Wilcoxon test for matched pairs)

In cats with chronic pancreatitis, basal pancreatic blood flow was reduced and pancreatic vascular resistance was increased. The normal pancreas autoregulated blood flow until portal pressure was > 15 mmHg. In cats with chronic pancreatitis, pancreatic blood flow was less than normal at all levels of portal pressure, and autoregulation was lost. In patients with chronic pancreatitis, portal hypertension may reduce pancreatic blood flow and contribute to progression of disease.

α_1-Antichymotrypsin inhibits lung injury induced by pancreatitis

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α_1-Antichymotrypsin (ACT) is a protease inhibitor that binds and neutralizes the leucocyte proteases elastase and cathepsin G, thus inhibiting neutrophil chemotaxis and degranulation. Neutrophil infiltration, which may result from an imbalance between leucocyte proteases and endogenous protease inhibitors, is central to the adult respiratory distress syndrome. The role of recombinant ACT in ameliorating lung injury associated with pancreatitis was evaluated.

Sprague–Dawley rats (400–500 g) were randomized to control (saline infusion) or caerulein-induced pancreatitis groups, and treated with saline or ACT (50 mg kg^{-1}). Myeloperoxidase level was used to monitor neutrophil infiltration in the lung, and wet:dry lung weight to measure pulmonary endothelial permeability. Lungs were also evaluated histologically.

Caerulein (5 $\mu g\, kg^{-1}\, h^{-1}$) induced pancreatitis in all animals, with an increase in mean(s.e.m.) serum amylase concentration from 1851(208) (control) to 5198(924) (pancreatitis) units ($P < 0·05$, Student's t test).

	Control ($n = 8$)	Pancreatitis ($n = 9$)	ACT ($n = 8$)
Myeloperoxidase units (units/g)	2·08(0·5)	7·8(1·1)*	4·68(0·7)*†
Wet:dry lung weight		12·8(3·3)	4·2(0·5)†

Values are mean(s.e.m.). *$P < 0·001$ *versus* control; †$P < 0·05$ *versus* pancreatitis (Student's t test)

These data show that pancreatitis induced significant pulmonary neutrophil influx and pulmonary microvascular leakage, which were both attenuated significantly by ACT. These data support the hypothesis that deficient endogenous protease inhibition may be responsible for the neutrophil-mediated lung injury seen in pancreatitis, and recombinant protease inhibitors such as α_1-antichymotrypsinogen may have a therapeutic role in inhibiting lung injury in pancreatitis.

Trypsinogen and prophospholipase A_2 activation, renal damage and disease severity in acute pancreatitis

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In acute pancreatitis, prophospholipase A_2 has been implicated in the production of renal damage. It has been noted previously that urinary trypsinogen activation peptide (TAP) and prophospholipase A_2 activation peptide (PLAP) concentrations relate to disease severity. In this study urinary TAP and PLAP levels were examined in eight patients with mild and in seven with severe acute pancreatitis, and were related to urinary concentrations of albumin and β_2-microglobulin as indicators of renal damage.

Patients with severe disease had significantly higher admission and peak TAP concentrations (95·7 per cent confidence interval (c.i.) 9·8–211 pmol TAP per mmol creatinine, $P = 0·009$, and 95·7 per cent c.i. 22·7–246 pmol TAP per mmol creatinine, $P = 0·007$, respectively). Only peak PLAP concentrations were significantly higher in patients with severe disease (95·7 per cent c.i. 109–957 pmol PLAP per mmol creatinine, $P = 0·003$). Admission and peak concentrations of albumin, but not of β_2-microglobulin, were significantly higher in patients with severe disease (95·7 per cent c.i. 1·82–22·1 mg albumin per mmol creatinine, $P = 0·018$, and 95·7 per cent c.i. 6·87–75·6 mg albumin per mmol creatinine, $P = 0·005$, respectively).

There was a significant correlation between the areas under the time–concentration curve for TAP and PLAP ($r = 0·81$) and for TAP and albumin, but not between PLAP and albumin ($r = 0·48$) or β_2-microglobulin ($r = 0·39$).

These results demonstrate that the degree of glomerular damage is related to the amount of trypsinogen activated. They do not support the theory that prophospholipase A_2 is an important factor in the production of renal damage.

Reduction of liver tumour growth and blood flow by octreotide

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Octreotide inhibits the growth of atypical liver tumour in rats. The aim of this study was to investigate the effects of octreotide on the growth of, and blood flow to, experimental liver metastases derived from colonic adenocarcinoma.

A colonic adenocarcinoma cell line (WB2054M) syngeneic to F_1 hybrid rats was used to induce liver tumour. Cells (4×10^6) were injected into the portal vein of 36 F_1 rats. Twelve rats were treated with octreotide (2 μg twice daily) for 4 weeks and 12 with saline as a control. At 4 weeks the rats were killed and the proportion of hepatic replacement by tumour was calculated as a percentage. In the remaining group of 12 rats with liver tumour, tumour blood flow was determined before and after an intravenous infusion of octreotide (0·05 μg min^{-1} for 10 min) using a dual radiolabelled microsphere technique.

There was a significant reduction (Mann–Whitney *U* test) in the median (range) percentage hepatic replacement in the octreotide-treated rats, 1·3 (0·6–4·7) per cent, compared with controls, 43·9 (30·1–55·2) per cent. There was also a significant reduction in the median (range) tumour blood flow following octreotide infusion, 0·37 (0·1–0·97) before *versus* 0·14 (0·04–0·45) ml min^{-1} g^{-1} after infusion.

The results indicate that octreotide inhibits the growth of hepatic tumour derived from colonic adenocarcinoma. Furthermore, octreotide reduced tumour blood flow, suggesting that this may, at least in part, be its mechanism of action in inhibiting growth.

DNA instability may define a small proportion of breast cancer pedigrees including those with a known germline p53 mutation

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It is suggested that the 17q familial breast cancer gene does not have a mechanism of action involving decreased DNA stability. It is possible, however, that other families with breast cancer, particularly those containing individuals with a germline mutant p53 gene, may have some general genetic instability that is revealed in the analysis of constitutional chromosome anomalies.

Peripheral blood lymphocytes from 18 breast cancer pedigrees, of which 11 were not obviously linked to a 17q gene, were analysed for constitutional chromosomal rearrangements. Sixteen of these families had a low frequency of such rearrangements (ten anomalies in 86 individuals). However, two pedigrees contained 13 individuals in whom a total of 26 separate constitutional chromosomal anomalies were detected. Both families contained cases of breast, ovarian, lung and other common malignancies diagnosed at mid to late age. Neither pedigree was 17q-linked but one contained individuals with a germline p53 mutation.

This suggests that individuals in a small proportion of cancer pedigrees may have identifiable genetic abnormalities at the microscopic level. A heritable DNA repair defect explains this phenomenon, but is unlikely to be a useful predictor of high-risk individuals since anomalies will be inherited regardless of genotype.

Genetic linkage analysis identifies women at greater than 60 per cent lifetime risk of breast cancer in seven of 15 families

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It is estimated that 6 per cent of all cases of breast cancer occur in patients with a strong genetic predisposition. Recent evidence has suggested that the likely site of a major breast cancer gene is the long arm of chromosome 17 (17q). Fifteen families with breast cancer have been subjected to linkage analysis using four genetic markers in this region. This analysis has revealed that the likelihood that a 17q gene is responsible for the familial distribution of breast malignancy is greater than 75 per cent in seven of these families (79·2, 85·5, 88·8, 92·3, 95·9, 99·2 and 99·9 per cent). Unaffected individuals with a greater than 60 per cent lifetime risk of breast cancer have been identified within these families by means of 17q marker analysis.

The present analysis localizes a major breast cancer gene to a small part of chromosome 17q12–21, 5–10 million base pairs in length, with a probability greater than 100 000:1. Meiotic recombination analysis suggests that the gene is flanked by genetic markers 42D6 and MFD188. This definition should aid in identification and sequencing of the gene, enabling women with a family history of breast cancer to undergo genetic screening without reference to labour-intensive linkage analysis which requires synchronous investigation of many relatives.

Expression of transforming growth factor β isoforms in human breast cancer

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The various isoforms of transforming growth factor (TGF) β may have effects on epithelial cell proliferation, and some of the effects of tamoxifen on human breast cancer could be mediated by induction of expression of TGF-β. Three closely related members, TGF-β_1, TGF-β_2 and TGF-β_3, have been identified and their biological activity may differ. The aim of the present study was to assess whether messenger RNA for the three isoforms of TGF-β could be identified in a series of human breast cancers.

Twenty-four human breast cancers were studied using an RNAse protection assay and specific riboprobes for TGF-β_1, TGF-β_2 and TGF-β_3. Tumours were considered positive for specific RNA expression if bands were identified on autoradiography with molecular weights corresponding to the appropriate full-length transcript. Of the 24 breast cancers, 22 (92 per cent) expressed TGF-β_1, 16 (67 per cent) TGF-β_2 and 21 (88 per cent) TGF-β_3. Sixteen cancers expressed all three TGF-β isoforms, six expressed one or two, and two did not express any (controls for a γ-actin probe in both cancers were positive).

This is the first report of TGF-β isoform expression in human breast cancer and will allow investigation of changes induced by tamoxifen treatment.

Allopurinol inhibits silicone-induced capsular contractility in a rat model

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Capsular contraction around silicone gel breast prostheses following postmastectomy reconstruction and augmentation mammoplasty remains a major clinical problem. Previous studies of capsular contraction have focused on microscopic assessment of capsules. Studies addressing the contractile potential of such capsules are few.

The capsules formed around subcutaneously implanted silicone rods (10 mm in diameter, 20 mm in length) in rats were assesssed 7, 14, 21, 28, 56 and 84 days after implantation by measuring capsular thickness and *in vitro* contractility. The results were compared with those from other groups of animals treated orally with the xanthine oxidase inhibitor allopurinol (50 mg per kg per day), commencing on the day of implantation.

Allopurinol significantly increased early capsular thickness compared with controls. In contrast, capsular contraction in the allopurinol-treated animals was reduced throughout the duration of the experiments.

	Capsular contractility*		
	Control (mg tension)	Allopurinol (mg tension)	P†
Time from implant (weeks)			
1 ($n = 10$)	65·6	35·5	<0·01
4 ($n = 5$)	11·4	5·6	0·05
12 ($n = 5$)	19·5	8·0	<0·035

*Median response to 4 mg mepyramine (a submaximal dose of a myofibroblast agonist); †Mann–Whitney *U* test

Allopurinol has been shown to slow the progression of myofibroblast-mediated conditions such as Dupuytren's contracture. In this rat model it inhibited silicone-induced capsular contractility, and may be a useful adjuvant therapy in the prevention of capsular contracture after breast implantation surgery.

Mood changes: why women request treatment for cyclical mastalgia

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It has previously been shown that women seeking treatment for severe cyclical mastalgia have cyclical mood variation. It has also been reported, but not explained, that only a minority of women with mastalgia seek treatment from their doctor.

Three groups of women were studied: 12 symptomless controls (group 1); 26 with moderate mastalgia not seeking treatment (group 2); and 21 with equivalent pain who requested treatment (group 3). Two anxiety and depression questionnaires (the Hospital Anxiety and Depression questionnaire and the Spielberger State–Trait Anxiety Inventory) were used. Subjects were tested at mid-follicular and mid-luteal phases of the menstrual cycle.

	Group 1	Group 2	Group 3
Follicular phase			
Anxiety	5·2(3·1)	8·4(4·7)	7·4(3·7)*
Depression	2·6(2·6)	4·7(3·4)	4·9(2·4)*
State anxiety	28·8(6·3)	36·8(12·0)	36·2(10·1)*
Luteal phase			
Anxiety	3·8(2·3)	7·8(5·2)	9·6(2·7)*
Depression	2·8(2·0)	5·2(2·8)	7·0(3·6)*
State anxiety	28·3(7·9)	39·5(13·2)	48·1(11·3)*
Anxiety trait	38·3(10·9)	43·2(10·3)	46·2(8·6)

Values are mean(s.d.). $^*P < 0{\cdot}05$ significant cyclical change *versus* group 1 (Mann–Whitney *U* test)

Women who present for treatment differ from symptomless women and those with cyclical pain in also having cyclical mood variation. This may explain why these women request treatment for mastalgia.

Assessment of DNA stability by means of chromosomal changes in stimulated cells in 17q breast cancer gene carriers and non-gene-carrying relatives

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Recent evidence has suggested that the mechanism of action of the heritable mutated tumour suppressor gene p53, which increases the risk of breast cancer as part of the Li–Fraumeni cancer family syndrome, involves a genetic predisposition to genome instability. To determine whether the phenomenon is responsible for familial breast cancer in general, seven families were examined in which breast cancer was found to be linked to a gene on chromosome 17q12–21 with a probability greater than 75 per cent.

A total of 1419 cultured stimulated peripheral blood lymphocytes from 25 family members unaffected by malignant disease were subjected to metaphase analysis for chromosomal rearrangements, variants, fragile sites and chromosomal loss and gain. Of these, 13 were breast cancer gene carriers as determined by 17q genetic marker analysis and 12 were age- and sex-matched non-gene-carrying relatives.

Gene carriers were found to be significantly less likely to exhibit expression of fragile sites ($\chi^2 = 4{\cdot}90$, $P < 0{\cdot}05$), chromosome loss ($\chi^2 = 8{\cdot}71$, $P < 0{\cdot}01$) and chromosome aberrations in general ($\chi^2 = 10{\cdot}87$, $P < 0{\cdot}001$) than non-gene carriers.

There is therefore no support for a hypothesis involving decreased DNA stability as a mechanism of action for the 17q gene. Indeed, increased stability appears to result from 17q gene mutation.

Accurate location of mammographic lesion boundaries using a genetic algorithm

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Much work has been carried out on the automatic diagnosis of breast lesions. However, none of the systems developed has achieved the accuracy of a trained radiologist. A major problem has been the accurate location of the lesion boundary. Systems that reliably locate a lesion do not accurately identify its boundary; an inexact lesion boundary degrades the quality of the subsequent diagnosis.

The work described in the present study sought to locate an exact lesion boundary from an approximate lesion location. The method employed a new search technique, the genetic algorithm, in which a more accurate lesion boundary was evolved from a less accurate initial boundary. This was achieved by scoring a set of candidate boundaries in terms of their edge strength and then selecting the strongest candidate. This new boundary was then used to generate additional candidates. The process was repeated until an acceptable boundary was produced.

In preliminary experiments, the genetic algorithm located 'exact' boundaries in 85 per cent of cases taken from a test set of 41 lesions.

Smoking may be implicated in the pathogenesis of the periductal mastitis complex

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The aim of this study was to determine whether smoking could be implicated in the aetiology of inflammatory breast disease by identification of the pathological features associated with smoking within the affected breast.

A retrospective clinical and pathological analysis of patients presenting with benign inflammatory breast disease was performed. A total of 58 patients were identified of whom 34 (59 per cent) were smokers. This proportion was significantly greater than the seven of 31 patients (23 per cent) in a non-inflammatory control group ($P < 0{\cdot}01$).

There was a highly significant association between smoking and the histological identification of a perivascular inflammatory infiltrate ($P < 0{\cdot}001$).

Thirty-one patients required further surgery for recurrent inflammatory disease, of whom 26 (84 per cent) were smokers. There was a positive correlation between the number of cigarettes smoked per day and the number of operations required ($P < 0{\cdot}01$). The presence of perivascular inflammation and anaerobic infection ($P = 0{\cdot}02$) were independent risk factors for disease recurrence as indicated by the total number of operations performed.

It is hypothesized that smoking may predispose to periductal inflammation by a primary perivascular reaction.

Swainsonine potentiates tumour susceptibility to cSF25-mediated antibody-dependent cell-mediated cytotoxicity

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The effectiveness of monoclonal antibody binding to tumour cells may be limited by antigenic expression. Swainsonine is an indolizine alkaloid that partially inhibits glycosylation processing. This may uncover glycoprotein molecules masked by sialic acid residues, thereby potentiating cellular antigenicity. The ability of swainsonine to augment target cell binding and lysis during antibody-dependent cell-mediated cytotoxicity was examined.

The colorectal cell line LS180 was incubated for 72 h with swainsonine at five concentrations and employed in an 18-h chromium-release assay using peripheral blood lymphocytes and a new anticolorectal chimeric antibody cSF25.

	Swainsonine concentration (μg ml^{-1})				
	0	1	2	5	10
No antibody ($n = 12$)	49(8)	52(11)	44(8)	48(10)	49(12)
cSF25 ($n = 12$)	248(21)	288(19)*	294(23)†	319(11)‡	293(22)§

Values are mean(s.e.m.) area under curve units. *$P = 0·028$; †$P = 0·006$; ‡$P = 0·001$; §$P = 0·007$ *versus* 0 μg ml^{-1} (paired *t* test)

The results show a dose-dependent increase in tumour cell lysis to a maximum of 5 μg ml^{-1}. This effect was antibody specific as there was no significant difference in the absence of antibody. Flow cytometric analysis confirmed an increase in cSF25 binding sites after incubation with swainsonine ($P < 0·01$). The present study has shown for the first time that swainsonine increases antibody binding sites in a human cell line, thus increasing tumour recognition and lysis by effector cells. This effect, coupled with the reported antitumour effects of swainsonine, makes it a promising therapeutic agent, particularly when used in combination with tumour-targeting monoclonal antibodies.

γ-Linolenic acid infusion in pancreatic cancer increases thymidine uptake and induces tumour necrosis factor release by peripheral blood mononuclear cells

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Polyunsaturated fatty acids such as γ-linolenic acid (GLA) have been shown to modify immune function and reduce tumour growth *in vitro* and in animal models. Fifteen patients with pancreatic cancer were given a 10-day intravenous infusion of GLA (lithium salt) in a phase I trial. On days 0, 5 and 10, peripheral blood mononuclear cells (PBMCs) were isolated. Spontaneous and lipopolysaccharide (LPS)-stimulated tumour necrosis factor (TNF) production was measured using the L929 bioassay. T cell blastogenesis in response to phytohaemagglutinin (PHA) was assessed using [^{3}H]thymidine uptake.

	Day 0	Day 5	Day 10
Spontaneous TNF release (pg ml^{-1})	750(200)	3 075(790)*	2 000(600)†
LPS-stimulated TNF release (pg ml^{-1})	4 750(827)	8 600(1212)*	7 475(1310)
Spontaneous [^{3}H]thymidine uptake (c.p.m.)	584(29)	934(111)*	2 204(463)*
PHA-stimulated [^{3}H]thymidine uptake (c.p.m.)	97 451(8085)	103 507(9833)	97 195(11 430)

Values are mean(s.e.m.). *$P < 0·01$; †$P < 0·05$ *versus* day 0 (Wilcoxon signed rank test)

GLA infusion resulted in a significant increase in both spontaneous and LPS-stimulated TNF release at day 5 and in spontaneous TNF production at day 10. [^{3}H]thymidine uptake by unstimulated PBMCs significantly increased during the GLA infusion. In contrast, PHA-stimulated [^{3}H]thymidine uptake remained unchanged. Lymphocyte subpopulations were assessed and remained unchanged.

It is concluded that GLA infusion in patients with pancreatic cancer results in an activation of the immune system, demonstrated by an increase in TNF release and spontaneous [^{3}H]thymidine uptake by PBMCs.

Lymphokine-activated killer cells from patients with colonic cancer are as effective as controls in lysing the multidrug-resistant colonic cancer cell line LoVoDx

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Multidrug resistance as mediated by p-glycoprotein is found in the majority of cases of colonic cancer, and may be responsible for the inherent insensitivity of this tumour to most chemotherapy. Controversy surrounds the susceptibility of multidrug-resistant (MDR) tumours to cell-mediated lysis. Lymphokine-activated killer (LAK) cells from patients with colonic cancer and from matched controls were studied.

Using a 4-h chromium-release assay the ability of these cells to mediate cell killing of the MDR colonic cancer cell line LoVoDx and parental non-MDR line LoVo was assessed. A range of effector:target ratios was used, from 100:1 to 12·5:1. Cell lines were grown in Ham's F12 medium with antibiotics, vitamin supplements and 10 per cent fetal calf serum. LoVoDx was maintained in medium that included 100 ng ml^{-1} doxorubicin, and grown in doxorubicin-free medium for 3 weeks before use in cytotoxicity assays. The continued expression of p-glycoprotein was checked by flow cytometry before use.

	Cytotoxicity (%)			
	Cancer cells ($n = 9$)		Controls ($n = 7$)	
Ratio	LoVo	LoVoDx	LoVo	LoVoDx
100:1	45·2(1·8)*	56·0(3·2)	48·7(1·9)*	53·6(1·0)
50:1	37·0(1·8)*	51·6(1·6)	39·4(1·4)*	45·0(2·2)
25:1	27·6(1·4)*	35·1(2·9)	27·4(1·1)*	34·1(0·4)
12·5:1	12·7(0·8)	11·8(1·2)	14·8(1·0)*	24·9(2·1)

Values are mean(s.e.m.). *$P < 0·05$ *versus* LoVoDx (two-way analysis of variance)

These results show that the MDR cell line was more sensitive to LAK-mediated lysis than the non-MDR line. LAK cells from both patients with cancer and controls were effective mediators of cancer cell killing. These data provide a rationale for the use of immunotherapy in MDR cancer.

P15E suppresses macrophage antitumour responses

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Macrophages occupy a central role in the defence against tumours. Studies have shown that tumour cells secrete a suppressive factor that may enable them to evade immune surveillance, thus contributing to the progression of malignant disease. This factor has proven difficult to isolate but a potential candidate is a protein found to have a significant degree of homology with the retroviral envelope protein P15E.

FG-10, a synthetic ten amino acid peptide of P15E, has been constructed in the authors' laboratory and shown to be potently immunosuppressive *in vitro*, and expressed by colorectal and gastric tumours. In the present study FG-10 was shown to suppress monokine secretion from activated macrophages (enzyme-linked immunosorbent assay (ELISA)), to downregulate major histocompatibility complex (MHC) class II antigen expression (flow cytometric analysis) and to inhibit the oxidative burst activity of macrophages.

	Monokine concentration (pg ml^{-1})*	
	Control	FG-10 (10^{-6} mol l^{-1})
TNF ($n = 11$)	3052(356)	2078(254)†
IL-1 ($n = 11$)	4201(453)	2526(443)†
IL-6 ($n = 11$)	8320(990)	5360(558)†

Values are mean(s.e.m.). TNF, tumour necrosis factor; IL, interleukin. *Determined by ELISA; †$P < 0·05$ *versus* control (Student's paired *t* test)

	Channel fluorescence*	
	Control	FG-10 (10^{-6} mol l^{-1})
MHC class II ($n = 6$)	595·0(116·9)	432·8(100·5)†

Values are mean(s.e.m.). *Determined by flow cytometry; †$P < 0·05$ (Student's paired *t* test)

The results suggest that host defence mechanisms are suppressed by P15E and may therefore provide a future therapeutic target.

Paracrine support of cancer cell growth: evidence for a stromal contribution to the metastatic cascade

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Evolution of a cancer to metastatic malignancy requires the active participation of its stroma. An *in vitro* model of breast cancer was established to test the hypothesis that there is a positive feedback loop of paracrine growth stimulation between fibroblasts and cancer cells.

Fibroblasts from benign and malignant breast tissue were established in short-term culture. They were cocultured with different breast cancer cell lines at different cell ratios. The two cell types were separated by a 0·4-μm polycarbonate filter (Costar); this allows free exchange of cytokines but prevents intermixing of the two cell types. Growth was measured in each compartment after 2, 4 and 6 days using the 3,4,5-dimethylthiazol-2,5-diphenyl tetrazolium bromide colorimetric assay. All experiments were carried out in serum-free medium.

Fibroblasts stimulated the growth of all three cancer lines (MCF7, MDA-MB231 and T47D) tested and fibroblast growth in turn was stimulated by the cancer cells. Partial fractionation of fibroblast-conditioned medium indicated a mitogenic component of molecular weight approximately 8 kDa.

This study provides evidence of a paracrine positive feedback loop between cancer cells and fibroblasts, and may indicate active recruitment of host connective tissue in the metastatic cascade.

Transforming growth factor β_1 is unlikely to mediate p53 abnormalities in breast cancer

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It has been proposed that an abnormal p53 gene in epithelial cells may induce tumorigenesis by reducing cellular responsiveness to the epithelial growth inhibitor transforming growth factor (TGF) β_1. Thus, p53 abnormalities could be associated with a high level of TGF-β_1 expression to which the cancer cells have become resistant. To test this hypothesis, p53 abnormalities and TGF-β_1 expression in primary untreated breast cancer were examined.

DNA was extracted from 41 invasive tumours and control DNA from the lymphocytes of each patient. Loss of a p53 allele in tumour DNA was examined using Southern blots and p53 mutations identified by direct DNA sequencing. TGF-β_1 gene expression was quantified by densitometry on Northern blots of RNA extracted from the same 41 tumours.

Loss of the p53 allele was identified in seven tumours (17 per cent) and p53 mutation in 31 (32 per cent). TGF-β_1 expression was detected in 33 tumours (80 per cent) and at high levels in 19 (46 per cent). There was no significant association between p53 abnormalities and TGF-β_1 expression. It is therefore unlikely that abnormal p53 has its tumorigenic effect through modifying TGF-β_1 expression in breast cancer.

Perioperative granulocyte–macrophage colony-stimulating factor activates macrophage-mediated antitumour mechanisms

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Perioperative immunosuppression may be associated with enhanced tumour growth. Granulocyte–macrophage colony-stimulating factor (GM–CSF) is a myelopoietic cytokine with potential antineoplastic effects. It was hypothesized that GM–CSF could potentiate host antitumour mechanisms in the perioperative period. In the first study 20 mice received Lewis lung carcinoma implants (5×10^5 tumour cells subcutaneously) and were randomized to receive perioperative GM–CSF (1 μg after operation) or saline vehicle control. Tumour volume and survival were then investigated. In the second study peritoneal macrophages were harvested from 30 tumour-bearing mice and studied for cell yields and (with or without GM–CSF coculture, 50 ng per ml per 10^6 cells) macrophage antitumour activity by superoxide anion (O_2^-) production.

	Tumour volume at 4 days (cm^3)	Survival rate at 21 days (%)	O_2^- (nmol)	Macrophages (%)	Neutrophils (%)
Control	0·77(0·3)	30	0·05(0·1)	45(1)	8·5(0·1)
GM–CSF	0·36(0·1)*	70†	0·42(0·1)‡	47(2)	17(1)§

Values are mean(s.e.m.) $^*P < 0{\cdot}005$; $^‡P < 0{\cdot}01$; $^§P < 0{\cdot}02$ (all *versus* controls, Student's *t* test); $^†P < 0{\cdot}02$ *versus* controls (χ^2 test)

Perioperative GM–CSF was associated with a reduction in tumour volume and prolonged survival that appeared to be mediated through enhanced neutrophil chemotaxis and increased activation of macrophage-mediated antitumour mechanisms. These results suggest a beneficial role for GM–CSF in the perioperative period by prolonging survival after laparotomy in the tumour-bearing host.

Role of cytokine-mediated cellular cytotoxicity in murine and chimeric antibody-dependent tumour lysis

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Antitumour antibody-dependent cell-mediated cytotoxicity (ADCC) may be partially mediated by the generation of tumour necrosis factor (TNF) α and interferon (IFN) γ. The chimeric monoclonal antibody cSF25 mediates high levels of ADCC against colorectal cancer. This antibody also produces significant monocyte activation compared with murine 17-1A (m17-1A) or chimeric 17-1A (c17-1A). Since monocytes produce both IFN and TNF, the present study investigated whether the superior ADCC of cSF25 may be blocked by anti-TNF and anti-IFN blocking antibodies (0·2 μg per well) compared with 17-1A-mediated ADCC. Peripheral blood lymphocytes were used in an 18-h chromium-release ADCC assay against the colorectal cell line LS 180.

	cSF25	m17-1A	Anti-TNF	Anti-IFN	Combined block
$n = 8$	—	140(34)	62(19)	129(34)	52(14)
P	—	0·007*	0·004†		0·005†
$n = 17$	256(21)	—	223(23)	236(26)	217(36)
P	0·0001*	—	0·0001‡		0·01‡

Values are mean(s.e.m.) area under curve units. * *Versus* no antibody; † *versus* m17-1A; ‡ *versus* cSF25 (paired *t* test)

The results show that the anti-TNF antibody significantly abrogated both m17-1A- and cSF25-dependent killing. In contrast, anti-IFN antibody failed to produce a significant reduction in cytotoxicity. Surprisingly, blocking TNF activity produced a mean(s.e.m.) reduction in cytotoxicity of 62(7) per cent with m17-1A but of only 22(4) per cent with cSF25. Therefore, although cSF25 produces significant monocyte activation and superior tumour cell lysis compared with m17-1A, the superior cell lysis mediated by this antibody is unlikely to be due to increased activity of TNF. This suggests that this monocyte activation induces cytotoxicity by a direct mechanism or via an as yet undetermined soluble mediator.

Effect of calcium channel blockers on the growth of human vascular smooth muscle cells from graft stenoses

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Intimal smooth muscle cell proliferation causing restenosis remains a major clinical problem after vascular intervention. Several animal models have shown calcium channel blockers to be effective at inhibiting this process. One small coronary restenosis trial in humans has shown equivocal benefit.

The effects of drugs from the three major classes of calcium channel blockers on the growth of cultured human vascular smooth muscle cells (VSMCs) derived from patients with graft stenosis and controls were investigated. VSMCs were cultured using standard techniques, growth rates of subcultured VSMCs were assessed at 0, 3, 7, 10 and 14 days, and the inhibitory effects of the antagonists measured.

	Inhibition of growth of VSMCs at 14 days (%)	
	Graft stenosis	Controls
Amlodipine (Dihydropyridine)		
1 μmol l^{-1}	5(2) ($n=5$)	5(1) ($n=5$)
10 μmol l^{-1}	24(1) ($n=5$)	34(2) ($n=5$)
Verapamil (Papaverine derivative)		
1 μmol l^{-1}	8(3) ($n=5$)	6(1) ($n=5$)
10 μmol l^{-1}	24(3) ($n=5$)	21(2) ($n=5$)
Diltiazem (Benzothiazepine)		
1 μmol l^{-1}	7 (5–9)* ($n=3$)	6 (5–6)* ($n=3$)
10 μmol l^{-1}	9 (5–12)* ($n=3$)	18 (5–20)* ($n=3$)

Values are mean(s.e.m.). *Range

VSMCs from patients with stenosis were significantly less sensitive to amlodipine (10 μmol l^{-1}) than controls ($P < 0·05$, Mann–Whitney U test). No significant difference was noted fpr verapamil or diltiazem. Controls were inhibited significantly more by amlodipine (10 μmol l^{-1}) than verapamil ($P = 0·01$, Mann–Whitney U test), which is consistent with the relative potencies of these drugs.

Significant growth inhibition occurred only at a 50-fold higher level than the therapeutic plasma level. These drugs are therefore unlikely to be of clinical value in the management of restenosis.

Effects of fibric acid derivatives on human vascular smooth muscle cell growth: a possible preventive therapy for restenosis

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Myointimal hyperplasia causes stenosis in 20 per cent of lower-limb grafts. The effect of fenofibrate, a putative platelet-derived growth factor (PDGF) antagonist, on the growth of human vascular smooth muscle cells (VSMCs) was investigated. Fenofibrate is rapidly metabolized to fenofibric acid (FFA) and reduced fenofibric acid (RFFA), which accounts for the circulating plasma level (100 μmol l^{-1}). VSMCs were cultured using standard techniques, growth rates assessed at 0, 3, 7, 10 and 14 days, and the effects of the antagonists measured. In separate experiments, inhibition of tritiated thymidine uptake in 15 per cent fetal calf serum (FCS)-supplemented medium and serum-free medium (SFM) containing 20 ng ml^{-1} PDGF was measured.

	Inhibition of growth curves at 14 days (%)	Inhibition of [^{3}H]thymidine uptake (%)	
		15% FCS ($n = 7$)	SFM plus PDGF ($n=7$)
Fenofibrate (100 μmol l^{-1}) ($n=12$)	47(2·4)	48(8)	64(8)
FFA (100 μmol l^{-1}) ($n=4$)	0(0·23)	27(8)	16(2)
RFFA (100 μmol l^{-1}) ($n = 4$)	0(0·19)	35(10)	16(5)

Values are mean(s.e.m.)

Fenofibrate produces significant inhibition of growth over 14 days ($P < 0·001$, paired t test), [^{3}H]thymidine uptake induced by serum ($P < 0·01$) and PDGF ($P < 0·001$, both paired t test). FFA and RFFA produce significant inhibition of [^{3}H]thymidine uptake induced by serum ($P < 0·02$ and $P < 0·02$ respectively, paired t test) and PDGF ($P < 0·001$ and $P < 0·05$ respectively, paired t test). FFA and RFFA do not produce inhibition in growth curves, but inhibit [^{3}H]thymidine uptake probably by delaying entry into the S phase of the cell cycle. Although fenofibrate is a potent inhibitor of VSMC growth, systemic administration is unlikely to inhibit restenosis because its metabolites do not inhibit VSMC proliferation. An alternative means of administration may therefore have to be considered.

Intimal hyperplasia is potentiated by graft damage and not inhibited by perindopril or trapidil

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The putative stimulatory effect of graft damage and inhibitory effects of angiotensin-converting enzyme (ACE) and platelet-derived growth factor (PDGF) antagonists on intimal hyperplasia have been studied in vascular grafts. Bilateral epigastric vein to femoral artery grafts were performed in 36 rats, in accordance with Home Office regulations. Four groups of 18 grafts (six per time interval) were studied: controls; traumatized (veins were immersed in distilled water and freeze–thawed before grafting); traumatized and treated with the ACE antagonist perindopril (1 mg kg^{-1} day^{-1}); and traumatized and treated with the PDGF antagonist trapidil (30 mg kg^{-1} day^{-1}). Vessels were assessed histologically at 1, 14 and 28 days. Intimal hyperplasia was measured at 28 days using image analysis.

	Intimal hyperplasia	
	Proximal anastomosis	Distal anastomosis
Controls	11·75(1·5)	8·71(1·3)
Traumatized	32·77(4·3)	19·51(2·9)
Perindopril	33·26(3·8)	22·55(5·2)
Trapidil	38·91(4·7)	21·17(2·6)

Values are mean(s.e.m.)

At day 1 traumatized grafts were completely denuded of endothelium and had severe medial architectural disorganization. Re-endothelialization was complete at 28 days. Control grafts had focal endothelial loss, which recovered by day 14, and better medial preservation. Intimal hyperplasia was significantly greater ($P < 0·05$, ANOVA) in the traumatized group compared with controls and was significantly greater ($P < 0·05$, ANOVA) at proximal compared with distal anastomoses in all groups. There was no difference in hyperplasia between the treated and untreated groups. This is consistent with graft damage contributing to intimal hyperplasia and hyperplasia not being reduced by perindopril or trapidil.

Thrombogenicity after angioplasty is abolished by restoration of the endothelial monolayer

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Platelet deposition, initiated by endothelial desquamation occurring during percutaneous transluminal angioplasty (PTA), causes acute arterial rethrombosis in up to 40 per cent of cases. The hypothesis that thrombogenicity at sites of PTA may be decreased by rapid re-endothelialization achieved by transluminal endothelial cell seeding was investigated.

Bilateral iliac angioplasty was performed in eight New Zealand White rabbits. One angioplasty site was isolated from the circulation and incubated with an endothelial cell suspension for 30 min using a double-balloon catheter. This technique achieved 50 per cent endothelial cell coverage of the damaged vascular surface. The contralateral angioplasty site was sham seeded with culture medium. The deposition of autologous ^{111}In-radiolabelled platelets on the two angioplasty sites was quantified 30 min after restoration of arterial flow and compared with platelet deposition on an undamaged segment of aorta.

Sample	Platelet deposition (per mm^2)
Sham seeded	$13·1 \times 10^4$
Endothelial seeded	$3·4 \times 10^{4*}$
Normal aorta	$3·6 \times 10^{4*}$

*$P = 0·014$ *versus* sham seeded (Wilcoxon signed rank test)

Platelet deposition was significantly greater on sham-seeded angioplasty sites than on normal aorta. Re-endothelialization of the angioplasty sites significantly reduced platelet deposition to a level indistinguishable from that of normal artery.

These results illustrate that rapid re-endothelialization of angioplasty sites, achieved by endothelial cell seeding, decreases subsequent thrombogenicity and may have clinical applications in reducing the rate of acute arterial reocclusion complicating PTA.

Selective haemodilution protects lung function in aortic surgery

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Postoperative lung dysfunction has been attributed to pulmonary sequestration of activated leucocytes and platelets during shock and major surgery. Isovolaemic preoperative 'selective' haemodilution was evaluated in 22 patients undergoing elective aortic surgery randomized to either haemodilution (11 patients) or control (11). A Haemonetics V50 aphaeresis machine was used to remove 30 per cent of circulating platelets, 20 per cent of leucocytes and erythrocytes to reduce the haemoglobin level to 10·5 g dl^{-1}. This concentrate was stored for reinfusion on wound closure. The arterial partial pressure of oxygen ($P_{\mathrm{aO_2}}$), arterial partial pressure of carbon dioxide ($P_{\mathrm{aCO_2}}$) and alveolar–arterial oxygen gradient ($\mathrm{A{-}a_{DO_2}}$) were measured before operation and at 6 days.

After operation mean(s.e.m.) $P_{\mathrm{aO_2}}$ fell in both controls and haemodiluted patients by 1·9(0·6) and 1·1(0·36) kPa respectively despite falls of 0·59(0·16) and 0·25(0·07) kPa in $P_{\mathrm{aCO_2}}$ ($P < 0{\cdot}05$ *versus* baseline, Student's *t* test). However, $\mathrm{A{-}a_{DO_2}}$ increased by 2·1(0·48) kPa in controls compared with only 0·33(0·36) kPa in patients undergoing haemodilution ($P < 0{\cdot}005$, Student's *t* test).

Selective haemodilution reduced the rise in $\mathrm{A{-}a_{DO_2}}$ (primarily affected by pulmonary shunting), demonstrating that postoperative pulmonary damage was related to platelet and leucocyte activation and was reduced by their removal.

Susceptibility to aortic degenerative disease is associated with type III collagen genotype

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Aortic aneurysm and aortoiliac stenosis are the two common degenerative diseases of the abdominal aorta; both are associated with smoking and atherosclerosis. Mutations in the type III collagen gene have been suggested as the basis for the familial tendency to abdominal aortic aneurysm (AAA).

Genomic DNA was prepared from the peripheral leucocytes of 145 patients with AAA, 84 with aortoiliac stenosis and 88 age-matched controls without aortic disease. DNA was analysed for two polymorphic sites and the Gly-619 mutation in the type III collagen gene. Distensibility of the abdominal aorta was assessed in 28 patients with AAA using M-mode ultrasonography to monitor aortic displacement during the cardiac cycle.

	AAA	Stenosis	Controls	*P**
Mean age (years)	73	68	70	<0·01†
Sex ratio (M:F)	41:9	37:13	18:7	<0·02†‡
Collagen III alleles (%)				
Thr-531	25·3	25·3	35·2	<0·05‡§
AvaII rare	28·8	18·6	27·2	<0·05♯§
Gly-619	0	0	0	

†AAA *versus* stenosis; ‡AAA *versus* controls; §stenosis *versus* controls; ♯stenosis *versus* AAA

Patients with the rare AvaII allele had a less distensible aorta than those not carrying this allele (median pressure–strain elastic modulus 41 and 25 N cm^{-2} respectively, $P < 0{\cdot}02$).

The presence of threonine at the 531st amino acid of type III collagen may provide some protection against susceptibility to aortic degenerative disease, while the AvaII mutation appears to be associated with aortic distensibility, the more distensible aortas being less susceptible to aneurysmal dilatation. There is no evidence that AAA is associated with the Gly-619 or any other common founder mutation in type III collagen.

Adjuvant iloprost does not improve results of local thrombolysis with recombinant tissue plasminogen activator

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Adjuvant antiplatelet therapy improves the efficacy of thrombolytic agents and is routinely used in the treatment of acute myocardial infarction. In peripheral thrombolysis, however, systemic antiplatelet therapy has been associated with an increased risk of bleeding. In the present study the use of a combination of recombinant tissue plasminogen activator (rtPA) and intra-arterial iloprost in peripheral thrombolysis was investigated.

A double-blind trial was undertaken in which 32 patients with recent lower-limb arterial occlusion treated with 0·5 mg h^{-1} rtPA were randomized to receive adjuvant iloprost at 2 g h^{-1} for 8 h or placebo. Clinical and radiological criteria of outcome, fibrinolytic parameters and *ex vivo* platelet function were assessed.

Lysis was successful in ten of 16 patients receiving iloprost and 11 of 16 given placebo ($\chi^2 = 0{\cdot}14$, $P = 0{\cdot}7$). The median time to lysis was 22·0 h in patients receiving iloprost and 22·4 h in those given placebo ($P = 0{\cdot}74$, Wilcoxon signed rank test). Only one major bleed was encountered in a patient receiving iloprost.

It is concluded that adjuvant intra-arterial iloprost does not improve the results of local thrombolysis with low-dose rtPA.

Thrombolysis of occluded infrainguinal vein grafts before operative intervention

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Vein graft (long saphenous vein: LSV) occlusion results in limb-threatening ischaemia. Despite graft surveillance the first presentation may be with occlusion. Revascularization is facilitated if the aetiology of the occlusion is known before operation. A consecutive series of 31 patients presenting at a mean(s.e.m.) of 13(6) days after occlusion of an infrainguinal LSV graft initially inserted for critical ischaemia were prospectively studied to assess the outcome of thrombolysis with intraluminal recombinant tissue plasminogen activator (rtPA).

Catheter placement failed in three patients but thrombolysis was successful within 24 h in 28, revealing an inflow problem in five, graft stenosis in eight, distal anastomotic stenosis in five and distal disease progression in seven. Three patients appeared to have no technical problem and underwent anticoagulation.

Successful revascularization was achieved in 18 patients (58 per cent) by operative or radiological intervention directed at the aetiology of the occlusion. This compares favourably with 43 per cent in a retrospective series who did not receive rtPA before surgery. Thrombolysis-related complications were confined to a false femoral aneurysm, a retroperitoneal haemorrhage and rhabdomyolysis-related renal failure.

The results suggest that intra-arterial thrombolysis with rtPA is a valuable preliminary investigation to determine the aetiology of LSV graft failure allowing directed intervention. A prospective randomized study is now required.

Sepsis decreases intestinal absorption of arginine

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Plasma arginine levels fall during sepsis and correlate with survival. Since intestinal amino acid absorption may be impaired, the intestinal absorptive function for arginine in two models of sepsis was investigated.

Arginine absorption was studied in rats 6, 12, 24, 48 and 72 h after caecal ligation and puncture, and 6 and 12 h after intraperitoneal (i.p.) injection of lipopolysaccharide (LPS) (*Escherichia coli* LPS 0127:B8, 1 mg per 100 g body-weight). Controls underwent sham laparotomy or received i.p. saline. All animals received 5 ml saline per 100 g body-weight subcutaneously, twice daily. Four 7-cm everted gut sacs were prepared from the proximal jejunum of each animal and filled with 800 μl Krebs bicarbonate buffer containing 100 μmol l^{-1} arginine (pH 7·4). Paired sacs (sepsis and control) were incubated at 37°C in flasks containing the same solution trace labelled with $[^3H]$arginine. After 60 min the sac contents were aspirated and arginine uptake determined using a scintillation counter.

	Time after induction of sepsis (h)				
	6	12	24	48	72
Sham	414(22)	354(13)	341(18)	313(17)	408(31)
Caecal ligation and puncture	379(13)	264(12)*	263(11)*	206(16)*	361(25)
Saline	377(14)	367(15)			
LPS	273(14)*	359(18)			

Values are mean(s.e.m.) arginine absorption (nmol per sac per h) of 24 sacs. *$P < 0·001$ *versus* control (Student's *t* test)

Induction of sepsis by caecal ligation and puncture or by i.p. LPS significantly impairs intestinal arginine absorption (system y^+ transporter). Recovery from sepsis leads to normalization of arginine absorption (72 h for caecal ligation and puncture, 12 h for LPS). Reduced arginine absorption coupled with increased utilization of this amino acid may explain the fall in plasma arginine levels during sepsis and its deleterious effects on survival.

Tumour necrosis factor increases release of plasminogen-activator inhibitor 1 by human peritoneal mesothelial cells

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Human mesothelial cells have been shown to synthesize plasminogen-activator inhibitor (PAI) 1 in inflamed peritoneal tissue. The aim of this study was to establish whether tumour necrosis factor (TNF) is a potential mediator of this response.

Confluent human mesothelial cells (LP9) were exposed to recombinant TNF-α (500 units ml^{-1}) for up to 18 h followed by recovery of the conditioned media and lysis of the cells. Media from both TNF-stimulated and control cultures were assayed for PAI-1 by enzyme-linked immunosorbent assay and cell lysates were assayed for protein by a dye-binding method. Immunohistochemistry confirmed the mesothelial origin of the cells and the presence of PAI-1 antigen.

TNF-α significantly increased the mean(s.e.m.) release of PAI-1 by mesothelial cells at 4 h (control 1·84(0·17) *versus* TNF 2·37(0·17) ng per μg protein; $P < 0·05$, ANOVA), 6 h (control 2·53(0·09) *versus* TNF 3·88(0·46) ng μg^{-1}, $P < 0·05$) and 18 h (control 0·5(0·02) *versus* TNF 1·04(0·11) ng μg^{-1}, $P < 0·05$).

This study suggests that TNF may be an important mediator of PAI-1 production by human mesothelial cells during peritoneal inflammation.

Discovery and characterization of a novel gastrin-releasing peptide receptor on human gastric and colonic cancer cell lines

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Bombesin, an amphibian peptide, has two mammalian homologues, gastrin-releasing peptide (GRP) and neuromedin B (NMB), both of which are demonstrable in the human gastrointestinal tract. Bombesin-like peptides are mitogenic and have been implicated in the pathogenesis of certain malignancies, especially small cell lung cancer. This study aimed to examine human gastrointestinal adenocarcinoma cell lines for the presence of receptors for these peptides.

Using ^{125}I-Tyr-4-radiolabelled bombesin as a radioligand and bombesin, GRP and NMB as competitors, the following cell lines were examined by standard displacement assays: HT29 and COLO320HSR for colonic cancer; and ST16, ST42, MKN45 and KatoIII for gastric cancer.

Displaceable binding was demonstrated only on ST42 and COLO320HSR. The relative affinity for the competitors was GRP greater than bombesin greater than NMB, indicating a GRP receptor. The receptor affinity and number were calculated by Scatchard analysis and were 0·5 nmol l^{-1} and 2000 sites per cell respectively.

The receptor was then cross-linked to ^{125}I-Tyr-4-radiolabelled bombesin using ethylene glycol-*bis*(succinimidylsuccinate) and sodium dodecylsulphate polyacrylamide gel electrophoresis was performed on the solubilized product. This revealed a novel single receptor protein with a molecular weight of 40 kDa, compared with the classical 80-kDa GRP receptor. Bombesin antagonists with a high affinity for this novel receptor may have therapeutic potential in gastrointestinal cancer.

Expression of p53 and DNA content in purified urothelial cells

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In bladder cancer, urothelial abnormalities distant from the primary tumour are associated with progression, but are difficult to detect. Flow cytometry of DNA content using bladder washings can detect such abnormalities, but is limited by contamination with other cells. This study aimed to improve analysis of bladder washings by selecting cytokeratin-positive cells. The tumour-suppressor gene protein p53 was also investigated.

Bladder washings were collected from 70 patients with bladder cancer. DNA was stained using propidium; cytokeratin and p53 were stained using antibodies LP34 and PAb1801. Samples were analysed on a FACScan (Becton–Dickinson).

There were significant differences between sorted and unsorted cells in DNA analysis. Of the sorted samples, 44 had diploid cells, four aneuploid cells and 22 both. Overexpression of p53 was significantly associated with abnormal DNA content (12 samples were p53 positive, of which nine were aneuploid and three diploid; Yates $\chi^2 = 7·04$, $P = 0·008$).

Sorting on cytokeratin content improved flow cytometry. Overexpression of p53 can be detected in bladder washings using flow cytometry and was associated with abnormal DNA. The use of sorted cells improves detection of abnormalities and may identify urothelial changes earlier and improve molecular biological studies by better definition of cell populations.

Fibrinolytic therapy inhibits pulmonary tumour seeding: a comparison of streptokinase and human recombinant tissue plasminogen activator

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The haemostatic system and the metastatic process are intimately inter-related. Electron microscopy studies in animal models have shown that tumour cell emboli arrest in the microcirculation within a fibrin–platelet mesh. The aim of this study was to compare the inhibitory effects of streptokinase with the more effective clot-lysing agent human recombinant tissue plasmingen activator (rtPA), on pulmonary tumour seeding in an animal model.

Three groups of ten female F344 rats were given 10^5 Mtln3 cells via tail vein inoculation under general anaesthesia. In addition, further intravenous treatments were administered as follows: group 1, no additional treatment (controls); group 2, streptokinase (30 000 units kg^{-1}) 30 min after tumour cell injection; and group 3, rtPA (5 mg kg^{-1}) 30 min after tumour cell injection. The animals were killed at 17 days and pulmonary tumour nodules assessed.

	Group		
	1	2	3
No. of nodules	55(5·2)	25(2·9)	27(6·1)

Values are mean(s.e.m.)

Streptokinase and rtPA significantly inhibited pulmonary tumour seeding ($P < 0·01$ group 1 *versus* 2, $P < 0·001$ group 1 *versus* 3; Mann–Whitney *U* test). There was no significant difference between groups 2 and 3.

Both streptokinase and rtPA inhibit pulmonary tumour seeding in this model. Greater fibrin specificity and its non-immunogenic nature make rtPA a potentially more suitable agent for antimetastatic treatment.

Experimental liver metastases and the reticuloendothelial system

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It has been suggested that stimulation of hepatic reticuloendothelial system (RES) activity may be the mechanism whereby octreotide inhibits the growth of hepatic metastases. To investigate this hypothesis the effects of octreotide and gadolinium chloride, a known inhibitor of the RES, on the growth and development of hepatic tumour were assessed.

Two groups of 12 BDIX rats received intravenous gadolinium chloride ($5\ \text{mg kg}^{-1}$) and two groups (controls) received saline. All animals then received an intraportal injection of 10^7 K12/Tr cells. Rats from each group received either 2 μg octreotide or saline subcutaneously, twice daily for 4 weeks, then the percentage hepatic replacement by tumour was determined.

At 4 weeks the median (range) proportion hepatic replacement of liver by tumour in the four groups was: saline and saline (control) 17·5 (5·7–24·2), saline and octreotide 0·6 (0–2·5), gadolinium chloride and saline 42 (21·2–68) and gadolinium and octreotide 11·2 (1·9–32·4) per cent.

These results indicate that RES blockade with gadolinium chloride significantly ($P < 0{\cdot}01$, Mann–Whitney U test) increases tumour growth compared with controls. Octreotide significantly inhibited tumour growth but is more effective in the absence of gadolinium. It appears that RES activity is important in the growth of liver metastases. The efficacy of octreotide may be partly dependent on a functioning RES system, but other mechanisms are also operating.

Targeting of 5-fluorouracil to the liver: evaluation of a novel disaccharide adduct

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Targeting of 5-fluorouracil (5-FU) to the liver of patients with hepatic metastases may maximize tumour kill, minimize systemic side-effects and possibly improve survival. The aim of this study was to compare the uptake of 5-FU and a novel 5-FU disaccharide (galactose and fructose) adduct by normal liver tissue and hepatic tumour in rats.

Hepatic tumour was induced in BDIXZ rats by intraportal injection of 10^7 K12/Tr adenocarcinoma cells. Groups of rats with hepatic tumour received 5 mg [^{14}C]5-FU or [^{14}C]5-FU adduct (22 mg) containing the same concentration of 5-FU and blood samples were removed at 10-min intervals. The rats were killed 1 h after administration of the 5-FU or adduct, the visceral organs removed, weighed and the radioactivity level measured using a scintillation counter.

The hepatic uptake of 5-FU and the adduct was not significantly different between the two groups of animals ($P > 0{\cdot}05$, Student's t test). However, the mean(s.e.m.) uptake of adduct by tumour tissue was four times greater than that of 5-FU (4226(190) *versus* 1003(190) c.p.m. per g, $P < 0{\cdot}001$). Conversely, the mean(s.e.m.) maximal blood level of the adduct was significantly less than that of 5-FU (57·9(0·65) *versus* 212·7(2·9) c.p.m. per ml).

The results of this study indicate that coupling of 5-FU to a simple carbohydrate containing a galactose moiety selectively targets the cytotoxin to hepatic adenocarcinoma and may therefore potentiate tumour kill and improve survival.

Tumour cell kinetics measured *in vivo* using 5-bromo-2′-deoxyuridine

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Tumour cell kinetics may help to predict outcome and determine treatment in patients with cancer. Previous methods of measuring tumour growth rates indicated the proportion of cells in different phases of the cell cycle, but gave no information about the rate of cell division. *In vivo* labelling with 5-bromo-2′-deoxyuridine gives this information, allowing estimation of the proportion of cells in S phase (labelling index: LI), the length of S phase (T_s) and the potential doubling time (T_{pot}). These parameters were calculated in 301 tumours of the breast, cervix, and head and neck.

Tumour	No.	Aneuploid (%)*	LI (%)*	T_s (h)*	T_{pot} (days)*
Breast	76	59	3·2	13·1	11·9
Cervix	120	71	9·5	12·1	4·4
Head and neck	105	72	8·0	13·7	6·2

*Values are medians

Breast tumours show markedly lower cell proliferation rates than the other tumours studied. Comparison with clinical staging showed that labelling index increased with increasing stage in cervical tumours only, but otherwise cell kinetic parameters were not related to staging information. Aneuploid tumours had a significantly higher labelling index than diploids in breast tumours, but not in the squamous tumour types. T_s was not correlated with LI.

Dynamic cell kinetic measurements can be made in over 90 per cent of tumour samples, and may indicate biological differences between different tumours and different tumour types.

Abnormal colonic epithelial proliferation in patients at risk for colorectal cancer

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In experimental colorectal carcinogenesis the first mucosal alteration is hyperproliferation despite normal histology. The aim of this study was to determine whether patients at high risk for colorectal cancer exhibit abnormal proliferation. Four groups were studied: patients with polyps (11), patients with colorectal cancer (eight), first-degree relatives of patients with colorectal cancer (seven) and normal controls (11).

Proliferation patterns in colorectal epithelium are demonstrated by marking cells in S phase of the cell cycle. Normal colonoscopic biopsies were incubated *in vitro* with 5-bromo-2′-deoxyuridine (BrdU). This thymidine analogue was detected in S phase cells using a monoclonal antibody to BrdU and standard immunohistochemistry. The proliferation patterns were expressed as labelling indices.

	Labelling index	
	Overall (%)	Upper fifth of crypt
Controls	5·6(0·5)	0·0(0·0)
Patients with polyps	9·2(1·0)*	0·7(0·3)*
Patients with colorectal cancer	8·7(0·7)*	0·4(0·8)
First-degree relatives	8·7(1·2)*	0·4(0·1)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* controls (Mann–Whitney U test)

Risk groups exhibit a significant increase in the overall labelling index and a significant shift of the proliferation zone towards the luminal surface of the crypt. Proliferation abnormalities may be used to identify high-risk patients requiring colonoscopic surveillance and to monitor chemoprevention studies.

Cytotoxicity of essential fatty acids: a novel therapeutic approach

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The essential fatty acids γ-linolenic acid (GLA) and eicosapentaenoic acid (EPA) are established in the treatment of mastalgia and exfoliative skin conditions. They have been shown to modulate cell proliferation in animal models. It is not yet known whether this activity may translate into practical therapy for human solid tumours.

The cytotoxic actions of EPA and GLA (at pharmacological concentrations of 100, 50 and 12·5 $\mu\text{g ml}^{-1}$) were studied *in vitro* on normally proliferating keratinocytes, virally immortalized cutaneous epithelial cells SVK14 and colonic carcinoma HT29. Cell growth was assessed by a colorimetric method using a methylene blue binding assay.

A dose-dependent inhibition of cell proliferation was observed in all three cell lines, with the deregulated cells being much more sensitive to the action of the fatty acids. The *Table* shows growth as a proportion of the control when measured by optical density of bound dye.

Fatty acid	Cell type	Fatty acid concentration (μg ml^{-1}) 12·5	25	50	100
GLA	Keratinocytes ($n = 3$)	0·9 (0·9–2·0)	0·9 (0·8–1·5)	0·7 (0·7–0·9)	0·9 (0·9)
EPA	Keratinocytes ($n = 3$)	0·7 (0·5–0·8)	0·5 (0·3–0·6)	0·2 (0·2–0·4)	0·2 (0·2–0·3)
GLA	SVK14 ($n = 3$)	1·2 (0·8–1·5)	0·8 (0·7–0·9)	0·4 (0·02–0·05)	0·05 (0·02–0·3)
EPA	SVK14 ($n = 3$)	0·7 (0·6–0·8)	0·6 (0·4–0·7)	0·3 (0·1–0·6)	0·07 (0·07–0·5)
EPA	HT29 ($n = 3$)	0·5 (0·2–0·5)	0·5 (0·2–0·5)	0·3 (0·2–0·5)	0·2 (0·2)

Values are median (range)

Inhibition of human cells by essential fatty acids suggests studies of their potential to modulate cell proliferation should be carried out.

Expression of the extracellular matrix protein laminin in Hirschsprung's disease

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Previous immunohistochemical and biochemical studies by the authors of the extracellular matrix proteins of the gut have shown increased laminin in the basement membrane of the smooth muscle layer in Hirschsprung's disease compared with normal gut.

In the present study, the steady-state messenger RNA level of the laminin subunits was quantified to determine whether the increased laminin in the basement membrane of smooth muscle is a direct consequence of increased expression. Northern blot hybridization was carried out on bowel specimens (containing proximal normoganglionic and distal aganglionic segments) from seven patients with Hirschsprung's disease and seven age-matched patients without.

Laminin was expressed in the form of B_1 and B_2 chains. Values of mRNA are given in the table as the ratio of steady-state mRNA and total RNA blotted on to the nylon membrane.

	Specimen Proximal normoganglionic	Distal aganglionic	Non-Hirschsprung's disease
B_1 chain	0·12 (0·028–0·67)	0·076 (0·018–0·17)	0·13 (0·02–0·28)
B_2 chain	0·07 (0·031–0·13)	0·12 (0·042–0·34)	0·13 (0·1–0·39)

Values are median (range)

There was no significant difference in the expression of steady-state mRNA of either B_1 or B_2 chain between Hirschsprung's disease and non-Hirschsprung's disease specimens ($P = 0·01$, ANOVA). The A chain was found to be absent in human bowel.

These results suggest that the increased laminin in the basement membrane of bowel in patients with Hirschsprung's disease is not related to increased expression and may be a result of abnormal turnover.

Release of arachidonic acid is increased in human colorectal cancer

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Arachidonic acid metabolites are strongly implicated in colorectal carcinogenesis and levels of arachidonic acid itself are increased in human tumours. Although it is known that the level of arachidonic acid is increased in tumour membrane lipids, it is not known whether metabolically active arachidonic acid is increased. Since the great majority of arachidonic acid is in membrane lipids and the free arachidonic acid pool is miniscule, the activities of phospholipase (PL) A_2 and diacylglycerol lipase (DGL), which release arachidonic acid, were measured. Tissue enzyme activities were measured in 18 colorectal cancers and normal mucosa using ^{14}C-radiolabelled substrates. The extent of tumour inflammatory infiltrate was determined by a myeloperoxidase (MPO) assay.

The results show that both PLA_2 and DGL activities were increased in cancer tissue. Although there was also an increase of MPO activity in cancer tissue there was no significant correlation between the activity of MPO and the activities of either PLA_2 or DGL in either tissue type (Spearman rank correlation).

Tissue activity	Colorectal cancer ($n = 8$)	Normal mucosa ($n = 18$)	P*
PLA_2 (pmol per h per mg protein)	8·9 (1·0–24·6)	4·4 (1·2–16·4)	0·006
DGL (pmol per h per mg protein)	49·9 (12·2–587·6)	19·5 (7·81–89·9)	0·020
MPO (units per mg protein)	0·65 (0·03–1·79)	0·07 (0·01–0·88)	0·01

Values are median (range). *Mann–Whitney *U* test

The present study indicates that there is increased release of arachidonic acid in human colorectal cancer and that this is not related to inflammatory tumour infiltrate. Given the role of arachidonic acid and its metabolites in carcinogenesis, this may have implications for therapy.

Hepatocyte growth factor/scatter factor: expression of receptors and effect on motility of human colonic cancer cells

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Hepatocyte growth factor (HGF)/scatter factor is a motogen for some cells. Its receptor is encoded by the c-*met* proto-oncogene. The aim of this study was to investigate the expression of HGF receptors (c-*met* protein) and the effects of HGF on the motility of a variety of human colonic cancer cells.

HGF receptor expression was determined on four human colonic cancer cell lines (HT29, HT115, HT55, HRT18) immunohistochemically by using a specific antihuman c-*met* protein antibody. The effects of HGF on cell motility were measured by both a colony-scattering assay and a dissociation assay from Cytodex-2 beads.

All four cell lines stained strongly for HGF receptors on their surface. The cell colonies were scattered by recombinant human HGF over a wide range of concentrations (1–20 ng ml^{-1}) and the effects were completely blocked by the presence of anti-HGF antibody. HT115 cells were the most sensitive tested. The cell dissociation assay also demonstrated the increased motility induced by HGF (shown as cell number dissociated from beads).

	Control	HGF (5 ng ml^{-1})	P*
HT115	39·1(7·1)	215·5(17·7)	<0·01
HT55	55·2(2·7)	280·5(31·5)	<0·01
HT29	40·0(5·4)	87·5(2·5)	<0·01
HRT18	18·2(3·3)	79·0(4·9)	<0·01

Values are mean(s.e.m.). *Student's *t* test

The HGF-induced cell dissociation from carrier beads was abolished by anti-HGF antibody.

It is concluded that human colonic cancer cells express HGF receptors and that HGF is a motility upregulator of these cells. HGF may therefore have a significant role in the invasiveness of colonic cancer.

Increased mucosal production of interleukin 8 in inflammatory bowel disease

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The cytokine interleukin (IL) 8 is an important mediator of the inflammatory response by its potent neutrophil chemoattractant properties. Although there may be severe local inflammation in ulcerative colitis (UC), serum IL-8 (sIL-8) levels are not always raised to reflect this process. The present study aimed to assess local (mucosal) production of IL-8 in inflamed and non-inflamed colon with simultaneous measurement of sIL-8.

Colonic biopsies were taken from patients with active UC ($n = 12$), inactive UC ($n = 6$), active Crohn's colitis ($n = 5$) and controls ($n = 12$). The mononuclear cells (MNCs) were isolated by mincing, followed by enzymatic digestion using collagenase and hyaluronidase. Isolated cells were incubated with or without lipopolysaccharide (LPS) at 10 μg ml^{-1} for 24 h in an anaerobic environment. The culture supernatant was stored at −70°C. Secreted and serum IL-8 levels were determined using enzyme-linked immunosorbent assay. IL-8 was detected in all the biopsies.

	MNCs (pg ml^{-1})	MNCs plus LPS (pg ml^{-1})
Active UC ($n = 12$)	6440(790)	7180(720)
Crohn's colitis ($n = 5$)	6330(980)	6560(880)
Inactive UC ($n = 6$)	1390(150)	1260(150)
Controls ($n = 12$)	760(120)	830(90)

Values are mean(s.e.m.)

IL-8 production from the mucosa of patients with active UC and Crohn's colitis was significantly greater than that from those with inactive UC and controls ($P < 0{\cdot}001$). Levels of sIL-8 were not significantly different within the groups. Increased IL-8 production locally in the inflamed colonic mucosa in active UC and Crohn's colitis may provide an explanation for the early recruitment of neutrophils and their subsequent activation.

Immunohistochemical analysis of p53 expression in anal squamous neoplasia

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The increased expression of p53 tumour suppressor protein has been shown to be a potential marker for malignancy in breast, colonic and oesophageal neoplasia.

A panel of two monoclonal antibodies (DO-1, DO-7) and one polyclonal antibody (CM-1) has been used to study p53 expression in normal anal epithelium, anal intraepithelial neoplasia (AIN) grades 1 and 2, AIN grade 3 from patients without demonstrable invasive disease, AIN grade 3 specimens from patients with invasive disease, and anal squamous cancers. Expression of p53 was not detected in normal anal epithelium ($n = 39$) or in AIN grades 1 or 2 ($n = 21$). The results of p53 immunostaining in specimens from AIN grade 3 and anal squamous cancer are shown.

	Group 1 (AIN grade 3, no invasion)	Group 2 (AIN grade 3, invasion)	Group 3 (anal cancer)
Positive staining	12 of 20 (60)	9 of 12 (75)	23 of 34 (68)

Values in parentheses are percentages

During a mean follow-up of 12 (range 3–18) months, two patients from group 1 with positively staining specimens subsequently developed anal squamous cancer.

These results suggest that it may be possible to use p53 protein as a marker of likely disease progession from AIN grade 3 to invasive tumour. Long-term follow-up of all patients with AIN grade 3 is required to confirm these results.

Omeprazole-induced hypergastrinaemia and experimental colorectal carcinogenesis

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Gastrin is trophic for colonic epithelium and exogenous pentagastrin can promote chemically induced rodent large bowel tumours. Hypergastrinaemia has been reported in patients with colorectal cancer and some human tumours express gastrin receptors. As acid suppression induces hypergastrinaemia, the present study was designed to investigate the influence of omeprazole on colorectal carcinogenesis in an experimental animal model.

A total of 40 female Sprague–Dawley rats were randomized to have either omeprazole (40 μmol kg^{-1}) or vehicle (0·25 per cent methyl cellulose) administered by daily oral gavage (1 ml) throughout the experiment. All animals received 12 consecutive weekly subcutaneous injections of azoxymethane (10 mg per kg per week) commencing at week 6. Serum gastrin levels were measured during week 5 and at death. One animal died during carcinogen administration and the remainder were killed at week 27.

Group	Serum gastrin level (ng l^{-1})*	Rats with tumour	No. of tumours per rat*
Omeprazole	1200 (600–3600)	12 of 19	1 (0–5)
Control	195 (135–300)	19 of 20	3 (0–10)
P	<0·001†	<0·02‡	0·002†

*Values are median (range). †Mann–Whitney U test; ‡Fisher's exact test

Tumour size, site distribution and histology were similar in the two groups. In this model, omeprazole-induced hypergastrinaemia does not promote colorectal carcinogenesis. In contrast, omeprazole-treated rats had a significantly reduced incidence of tumour development. The mechanism of this is uncertain and is currently under investigation.

Ileal pouch–anal anastomosis: continuous ambulatory measurement of pouch–anal coordination

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Although restorative proctocolectomy (RPC) is now a well established technique, the ideal method of constructing the ileal pouch–anal anastomosis remains controversial. The aim of this study was to investigate the internal anal sphincter and whether or not coordinated activity exists between the ileal reservoir and sphincter. Four groups of patients have been compared: normal controls (group 1) and those undergoing RPC with mucosal proctectomy and endoanal anastomosis (group 2), end-to-end anastomosis (group 3), and end-to-end anastomosis following stump eversion (group 4). Activity was measured over 180 min using continuous ambulatory manometry (2MB Digitrapper; Synectics).

	Group 1	Group 2	Group 3	Group 4
No. of patients	19	13	22	14
Basal activity	19	5†	22	14
Sampling (episodes per h)*	5·6 (1–30)	0 (0–30)‡	4·8 (1–48)	2·1 (0–6·3)

*Values are median (interquartile range). †$P < 0{\cdot}01$ (group 2 *versus* groups 1, 3 and 4); ‡$P < 0{\cdot}05$ (group 2 *versus* 4)

RPC with mucosectomy and endoanal anastomosis impairs the physiology of the anal sphincter. End-to-end anastomosis preserves the basal activity and coordination of the anal sphincter but has been criticized for retaining a variable amount of rectal mucosa. RPC with stump eversion was designed to prevent this possibility by allowing direct vision of the everted anal stump. The present results show that sphincter damage is less following stump eversion than for mucosectomy and endoanal anastomosis, with preservation of basal activity in all patients and persisting, though reduced, sampling episodes.

Rectal motor activity and recovery of continence after resection rectopexy for prolapse

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High-pressure rectal motor activity resulting in rectoanal inhibition has been described as a source of incontinence in patients with rectal prolapse. A total of 18 patients with prolapse and faecal incontinence (14 women, median age 57 years) were assessed before and 4–18 months after rectopexy by ambulatory manometry to determine whether recovery of continence after surgery is associated with cessation of this rectal motor activity.

The median (range) preoperative resting rectal pressure was 26 (14–38) cmH_2O and that of the anal pressure 38 (18–68) cmH_2O. Rectal motor activity (maximum 128 cmH_2O, median 54 cmH_2O, duration 1·5–8 min) associated with a fall in anal pressure to 5–41 cmH_2O was observed in all patients during daytime recordings but not during sleep. Eight patients noted that their prolapse appeared or that there was a desire to open their bowels during this activity.

The median (range) postoperative rectal pressure was 23 (14–32) cmH_2O ($P > 0{\cdot}05$) and anal pressure 55 (20–74) cmH_2O ($P < 0{\cdot}01$). Sixteen patients were continent for liquids and solids. Prolonged high-pressure rectal motor activity associated with rectoanal inhibition was no longer observed.

Restoration of continence following rectopexy for rectal prolapse is associated with the disappearance of prolonged episodes of rectoanal inhibition.

Magnetic resonance imaging in assessment of anal fistula

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The success of surgery for fistula *in ano* depends on accurate assessment. Preoperative imaging techniques used to help in fistula assessment have to date been disappointing. The accuracy of magnetic resonance imaging (MRI) in delineating anal fistula has been studied prospectively, comparing the scan interpretations with the clinical assessment of the fistula at subsequent operation. The surgeon was unaware of the scan results. A total of 35 patients (26 men, nine women) of mean age 41 (range 24–67) years with a clinical diagnosis of anal fistula entered the study. The mean time interval between scan and surgery was 29 (range 1–136) days.

	Agreement		Disagreement		Concordance (%)
	M+/S+	M−/S−	M+/S−	M−/S+	
Primary track					
Superficial/ intersphincteric	6	28	0	1	97
Trans-sphincteric	19	13	2*	1	91
Sinus	5	29	0	1	97
Secondary extension					
Intersphincteric	5	29	1	0	97
Ischiorectal	10	23	1	1	94
Supralevator	9	25	1*	0	97

M, MRI scan interpretation; S, surgical assessment. *The subsequent clinical course has shown MRI to have been correct

MRI is at least as accurate as experienced colorectal surgeons in assessing anal fistula, and should be used in the assessment of 'difficult' or recurrent fistula.

Pouchitis: a failure of butyrate oxidation

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The aetiology of pouchitis is unknown. Butyrate is the major fuel source for colonic mucosa and in ulcerative colitis (UC) there is a failure to utilize it. If this defect is present in the ileum of patients with UC it may lead to pouchitis. Biopsies (three for each fuel source) taken from the terminal ileum of patients with UC undergoing restorative proctocolectomy were incubated with [^{14}C]glucose, [^{14}C]glutamine or [^{14}C]butyrate. The evolved [^{14}C]carbon dioxide was quantified by liquid scintillation counting and the substrate flux to carbon dioxide calculated. Control biopsies were obtained from patients undergoing ileostomy formation.

	Normal ileum	Ileum in UC
Glucose ($n = 8, 7$)	541 (224–1127)	746 (175–3049)*
Glutamine ($n = 8, 7$)	4257 (1018–8713)	4236 (970–8327)*
Butyrate ($n = 8, 7$)	26 624 (11 813–38 810)	7495 (2424–13 323)†

Values are median (95 per cent confidence interval) expressed in pmol per mg tissue per h. *$P > 0{\cdot}05$; †$P < 0{\cdot}05$ (Mann–Whitney U test)

Mucosa from the normal terminal ileum is capable of oxidizing butyrate in greater quantities than glutamine or glucose. The ability of terminal ileal mucosa in UC to oxidize butyrate is significantly impaired. This metabolic defect may reflect the same pathological mechanisms that occur in UC and explain why pouchitis is much more common in colitic pouches than in those in familial adenomatous polyposis.

Pouches in patients with familial adenomatous polyposis are not at increased risk of neoplasia

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Restorative proctocolectomy in patients with familial adenomatous polyposis (FAP) abolishes the risk of rectal carcinoma but it has been feared that with time the pouch might itself be at increased risk of cancer. The development of ileal pouch adenomas in patients with FAP was compared with the number of ileal adenomas histologically detected at the time of primary colonic surgery.

A total of 38 patients with pouches for FAP were available for follow-up since 1977 (mean follow-up 4·6 years). In five patients ileal pouch adenomas have developed at a mean of 4·3 years from reservoir construction. Two patients have developed adenomas in relation to residual large bowel mucosa. The resected portion of terminal ileum from 203 patients with FAP undergoing primary colonic surgery has been examined histologically. The ileum was normal in 143 cases, showed lymphoid hyperplasia in 42 and tubular adenoma in 18.

There does not seem to be a markedly increased risk of pouch adenoma in FAP and the operation remains oncologically safe.

Internal anal sphincter electrical frequency is related to anal canal slow but not ultraslow waves

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Previous investigations of anal canal slow and ultraslow pressure waves have failed to show a relationship with the electrical slow wave of the internal anal sphincter (IAS) electromyogram (EMG). To elucidate whether such a relationship exists, mid- and upper anal canal pressures and IAS EMGs were recorded using a Gaeltec recorder in 15 normal patients and ten with anal fissure. The recordings were then analysed using fast Fourier transform waveform analysis.

Nine of the normal subjects had slow waves; six patients with fissure exhibited ultraslow waves. In the normal patients the median (range) slow-pressure wave frequency in the mid-anal canal was 0·37 (0·30–0·42) Hz and in the upper anal canal 0·32 (0·28–0·42) Hz. The median (range) IAS EMG frequency (0·35 (0·30–0·41) Hz) correlated with mid-anal canal frequency ($r_s = 0{\cdot}75$ (95 per cent confidence interval (c.i.) 0·18–0·95)) but correlated more closely with upper anal canal frequency ($r_s = 0{\cdot}94$ (95 per cent c.i. 0·72–0·99)). In patients with fissure the ultraslow wave frequency was 0·070 (0·054–0·106) Hz; the IAS EMG frequency (0·38 (0·33–0·45) Hz) bore no relationship to this. The slow waves seen in anal pressure and IAS EMG recordings are directly related and seem likely to be neurogenic in origin. The anal ultraslow waves are unrelated to the IAS EMG and may be myogenic in origin.

Rectal mucosal proliferation after colectomy and ileorectal anastomosis in familial adenomatous polyposis

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Rectal polyps regress and the incidence of rectal cancer decreases after total colectomy and ileorectal anastomosis (IRA) in patients with familial adenomatous polyposis (FAP).

Biopsies of apparently normal rectal mucosa were taken from 14 patients with FAP (seven female, seven male; mean age 26·5 years) before IRA and at 6 weeks, 6 months and 1 year after surgery. Mucosal proliferation was assessed by flash-labelling with 5-bromo-2'-deoxyuridine (BrdU) and labelled cells visualized by immunohistochemistry.

	Median rectal labelling index (%)	P*
Before colectomy	13·2	—
6 weeks	8·2	<0·05
6 months	6·6	<0·01
1 year	6·9	<0·01

* *Versus* before colectomy (Wilcoxon signed rank test)

As controls, two patients undergoing IRA for constipation and two having IRA for multiple cancers were also studied with precolectomy and postcolectomy rectal biopsies. Patients with multiple tumours showed similar results to those with FAP; in contrast, patients with constipation have low precolectomy cell proliferation (mean(s.e.m.) 8(0·1) per cent) and no significant change with surgery.

Patients who are not at risk of cancer show similar rectal mucosal proliferation to the present control and postcolectomy at-risk patients. The postsurgical reduction in mucosal proliferation probably explains polyp regression in the rectal stump, but the mechanism is unknown.

Analysis of deaths in familial adenomatous polyposis treated by colectomy and ileorectal anastomosis

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Patients with familial adenomatous polyposis (FAP) treated with total colectomy and ileorectal anastomosis (IRA) face an uncertain future. The risk of death in 222 such patients has been quantified using life-table analysis.

There were 134 men and 88 women with a mean follow-up of 14·2 (range 1–44) years of whom 53 have died. Comparison with an age- and sex-matched group from the general population gives an expected number of deaths of 15·8 and a relative risk of dying of 3·35 (95 per cent confidence interval 2·51–4·39), which is a significantly increased risk.

The main causes of death are: malignancy (29 patients) (55 per cent) (11 died from upper gastrointestinal adenocarcinoma); desmoid disease (five) (9 per cent); and perioperative mortality (five) (9 per cent). Women are at greatest risk (relative risk 4·93 *versus* 2·81 for men) as are those <55 years old. Advances in screening, surveillance and surgery have not been reflected by improvements in outlook over time (simple regression analysis $r^2 = 0·03$, $P = 0·16$).

Patients with FAP treated by IRA are at a significant survival disadvantage in comparison with the general population; this information should be available to all parties at prenatal testing.

Recovery of the internal anal sphincter after restorative proctocolectomy

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To investigate the role of the internal anal sphincter (IAS) in the gradual return of continence after restorative proctocolectomy, the IAS was prospectively assessed using concentric needle electromyography (EMG) and manometry in 12 patients (eight male, median age 34 years) undergoing a one-stage stapled procedure for chronic ulcerative colitis.

The median (range) preoperative IAS EMG frequency was 29 (26–32) cycles per min (c.p.m.) and resting anal pressure 98 (78–110) cmH_2O. Induction of anaesthesia resulted in transient IAS EMG inhibition and a fall in resting pressure which recovered to preoperative values within 30 min. Colonic and rectal dissection did not adversely affect IAS activity. Transanal stapling resulted in reduction of the IAS EMG frequency (median 12 c.p.m., $P < 0·003$) and a fall in median resting pressure to 36 cmH_2O ($P < 0·001$).

Follow-up revealed gradual recovery of the IAS median EMG frequency: at 7 days it was 14 c.p.m. ($P > 0·05$), at 4 months 19 c.p.m. ($P < 0·05$) and at 9 months 22 c.p.m. ($P < 0·03$). Resting anal pressure also recovered gradually to 44 cmH_2O at 4 months ($P < 0·05$) and 56 cmH_2O at 9 months ($P < 0·01$). Frequency of defaecation decreased from nine to four per 24 h.

Internal sphincter recovery following restorative proctocolectomy is gradual and the sphincter does not return to preoperative activity up to 9 months after surgery.

Splenectomy predisposes to systemic candidiasis through defective phagolysosome formation

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Postsplenectomy infectious sequelae may be fatal but the mechanisms of such conditions are unclear. It was hypothesized that peritoneal macrophage antimicrobial function is abnormal after splenectomy and that this may predispose to increased mortality from the fungal pathogen *Candida albicans*.

In the first (*in vivo*) study, female CD-1 mice were randomized to control, laparotomy or laparotomy plus splenectomy, and inoculated with *C. albicans* (10^7 organisms intraperitoneally) and mortality was investigated. In the second (*in vitro*) study, mice were randomized to control, laparotomy or laparotomy plus splenectomy groups. After 24 h, peritoneal macrophages were harvested and studied for antifungal activity, including: percentage macrophage ingestion of *Candida* and vacuolar sealing of *Candida* within macrophages; percentage *Candida* killing; and superoxide anion (O_2^-) generation, the mechanism by which *Candida* are killed.

Group	O_2^- (nmol)	*Candida* ingestion (%)	*Candida* killing (%)	Unsealed vacuoles (%)	Survival rate (%)
Control	0·02(0·01)	32(1)	28(4)	55(1)	87
Laparotomy	0·03(0·00)	17(2)	19(3)	77(3)	80
Laparotomy plus splenectomy	0·15(0·03)*	10(2)*	13(3)*	94(2)*	53*

Values are mean(s.e.m.). *$P < 0·05$ *versus* controls

Splenectomy was associated with a significantly higher mortality rate from *Candida* infection compared with controls ($P < 0·05$). This may have resulted from splenectomy-induced defective phagocytosis of *Candida* and depressed *Candida* killing but increased superoxide release in response to the pathogen. This discrepancy between decreased killing and increased superoxide release may result from increased leakage of superoxide from more unsealed vacuoles in the splenectomy group. Thus, splenectomy may predispose to *Candida*-induced mortality through defective peritoneal macrophage intracellular *Candida* killing while enhancing the release of superoxide extracellularly from unsealed vacuoles, causing host tissue injury.

Autoimmunomodulation by alterations in monocyte major histocompatibility complex class II expression

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Studies have shown that profound reductions in monocyte major histocompatibility complex (MHC) class II human leucocyte antigen (HLA) DR antigen expression after trauma and surgery are associated with infective sequelae. However, correction of this downregulation using interferon γ has been detrimental in animal studies and of questionable benefit in human trials. In an attempt to mimic the inflammatory insult of surgery *in vitro*, monocytes from 21 patients undergoing elective major surgery were cultured with endotoxin; HLA-DR and CD14 (lipopolysaccharide binding protein (LPS-BP) receptor) expression was measured by flow cytometry. HLA-DR and CD14 expression was also measured on circulating monocytes from the patients before and on the first day after operation.

	Cultured monocytes		Circulating monocytes	
	Control	Endotoxin	Before operation	After operation
HLA-DR	2363(337)	821(242)	164(20)	73(12)
CD14	1193(109)*	1469(222)†	139(7)‡	138(15)†

Values are mean(s.e.m.) mean channel fluorescence. $^*P < 0{\cdot}0001$; $^\dagger P$ not significant; $^\ddagger P < 0{\cdot}02$ (paired *t* test)

There were no postoperative infective complications; the observed reduction in monocyte HLA-DR expression associated with surgery occurred in all subjects. Likewise, endotoxin brought about similar alterations in HLA-DR expression in cultured monocytes. CD14 expression was unaffected in either instance. Because proinflammatory cytokine secretion from monocytes is regulated by an interaction of endotoxin with MHC class II antigens, moderate postoperative reductions in HLA-DR expression may be beneficial by averting the development of vicious cytokine cascades. Only when the true implications of altered postoperative phenotypes are realized will the use of immunomodulators be safe and advantageous.

Neutrophil hypochlorous acid generation predicts sepsis after surgery

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Polymorphonuclear neutrophil (PMN) respiratory burst dysfunction after surgery exposes patients to the risk of sepsis. Since PMN-derived hypochlorous acid (HOCl), a product of the respiratory burst, is a vital antimicrobial mechanism, evidence was sought of PMN HOCl generation dysfunction in a consecutive series of 38 patients undergoing gastrointestinal resection. Septic outcome was evaluated according to the criteria of Bone *et al.*[1] and patients underwent an uncomplicated postoperative course ($n = 28$) with no deaths, or a septic postoperative course ($n = 10$) with four deaths from sepsis. No significant differences were noted between the groups regarding preoperative age, weight, incidence of malignancy and sepsis. PMNs were isolated (density-gradient centrifugation) from peripheral blood samples harvested before operation and on days 1 and 6. The kinetic profile of HOCl generation was measured by 5-thionitrobenzoic acid (TNB) oxidation (412 nm).

	Time (min)				
	10–15	16–20	21–25	26–30	31–35
No sepsis					
Before operation	0·87(0·06)	0·89(0·05)	0·83(0·04)	0·75(0·03)	0·65(0·03)
Day 1	0·55(0·06)*	0·53(0·06)*	0·53(0·05)*	0·51(0·05)*	0·45(0·04)*
Sepsis					
Before operation	0·46(0·08)	0·46(0·09)	0·43(0·07)	0·42(0·06)	0·37(0·04)
Day 1	0·94(0·09)*	0·96(0·08)*	0·89(0·06)*	0·83(0·05)*	0·74(0·04)

Values are mean(s.e.m.) HOCl generation expressed as nmol per 10^6 PMNs $^*P < 0{\cdot}05$ *versus* baseline (ANOVA)

In patients without postoperative sepsis, PMN HOCl kinetics were significantly depressed on day 1 and returned to baseline by day 6 (data not shown). However, patients with sepsis who had activation of the respiratory burst by day 1 subsequently developed a sepsis response. It is concluded that measurement of PMN activation may allow prediction of patients destined to develop postoperative sepsis and that depression of PMN respiratory burst function may be a normal postoperative phenomenon.

1. Bone RC, Fisher CJ, Clemmer TP *et al.* Sepsis syndrome: a valid clinical entity. *Crit Care Med* 1989; 17: 389–93.

Tumour necrosis factor induces pulmonary injury dependent partly on neutrophils

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Tumour necrosis factor (TNF) α is a mediator of septic shock and has been identified in bronchoalveolar lavage of patients with respiratory distress. *In vitro*, TNF potently stimulates polymorphonuclear neutrophils (PMNs) to injure endothelium. The mechanism by which TNF induces pulmonary injury was tested.

In the study, 1000 units ($n = 9$) or 5000 units ($n = 9$) TNF was aspirated into the right middle lobe of anaesthetized rats (the PMN^+ group). After 3 h, bronchoalveolar lavage was performed to count PMNs that had migrated into the alveolar space and to assess protein leak. The sham animals ($n = 11$) were aspirated with saline. Further animals ($n = 19$) were treated with selective antineutrophil antiserum (PMN^- group) or protein synthesis inhibitor ($n = 18$) (Act D group).

	PMN count ($\times 10^4$ per ml)	Lavage protein ($\mu\text{g ml}^{-1}$)
Sham group	5(1)	131(48)
1000 units TNF		
PMN^+	18(2)*	363(62)*
PMN^-	5(1)†	196(48)†
PMN^+ plus Act D	6(1)†	124(64)†
5000 units TNF		
PMN^+	68(5)*	639(81)*
PMN^-	5(1)†	330(87)†
PMN^+ plus Act D	6(1)†	702(138)*

Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* sham group; $^\dagger P < 0{\cdot}05$ *versus* PMN^+ in the same group

Aspiration of 1000 units TNF led to alveolar migration of PMNs that correlated with protein leak ($r^2 = 0{\cdot}76$, $P < 0{\cdot}01$). Permeability was reduced by selective neutropenia (PMN count 10 per cent of baseline, $P < 0{\cdot}01$) and by Act D. Aspiration of 5000 units TNF induced similar changes but PMN migration and protein did not correlate ($r^2 = 0{\cdot}16$, $P = 0{\cdot}22$). Neutropenia only partially reduced protein leak.

The results indicate that TNF induces lung injury dependent partly on PMNs via protein synthesis.

Oxygen radicals and elastase in lung injury induced by tumour necrosis factor

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Tumour necrosis factor (TNF) α is a mediator of sepsis and is found together with polymorphonuclear neutrophils (PMNs) in bronchoalveolar lavage of patients with septic shock. Because TNF induces lung injury dependent partly on PMNs, the PMN products oxygen radicals and elastase were investigated in acute lung injury induced by aspiration of TNF in the rat.

Anaesthetized rats were treated with saline ($n = 6$), the oxygen radical scavengers superoxide dismutase/catalase (SOD/Cat) ($n = 7$) or PMN elastase inhibitor methoxysuccinyl-L-Ala-L-Ala-L-Pro-L-Val-chloromethylketone (MAAPV) 30 min before 5000 units TNF ($n = 6$) or saline ($n = 6$) was aspirated into the right middle lobe. After 3 h, bronchoalveolar lavage was performed to count PMNs in the alveolar space and to assess protein leakage.

	PMN count ($\times 10^4$ per ml)	Lavage protein ($\mu\text{g ml}^{-1}$)
Sham group	5(1)	132(12)
TNF (saline)	86(16)*	1125(172)*
TNF (SOD/Cat)	46(5)*†	680(86)*†
TNF (MAAPV)	20(4)*†	1110(232)*

Values are mean(s.e.m.). $^*P < 0{\cdot}05$ *versus* sham group; $^\dagger P < 0{\cdot}05$ *versus* TNF (saline)

Aspiration of TNF led to neutrophil migration into the alveolae together with an increase in lavage protein. Both SOD/Cat and MAAPV reduced PMN migration but only the former reduced protein leakage.

The results indicate that TNF aspiration leads to lung injury associated with alveolar migration of PMNs. PMN movement requires oxygen radicals and elastase but only oxygen radicals are involved in the protein leakage. Such mechanisms may operate in septic shock.

Granulocyte–macrophage colony-stimulating factor is protective against intra-abdominal sepsis after trauma

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The myelopoietic cytokine granulocyte–macrophage colony-stimulating factor (GM–CSF) may enhance immune mechanisms directed against bacterial infection. Injury is associated with an increased incidence of such infection. This study hypothesized that GM–CSF may have immunostimulatory properties in the injured host predisposed to infection. Female CD-1 mice (6–8 weeks old) underwent right hindlimb amputation, were randomized to receive either GM–CSF (20 mg per kg body-weight per day) or saline vehicle control intraperitoneally for 5 days and were analysed in two studies. In the first study, mice ($n = 20$ per group) underwent caecal ligation and puncture and mortality rates were investigated. In the second study, mice ($n = 25$ per group) were killed and peritoneal cells harvested for neutrophil influx and macrophage superoxide anion (O_2^-) production, and tumour necrosis factor (TNF) and nitric oxide (NO) release. Systemic bacterial growth was also assessed.

	Neutrophil influx (%)	O_2^- (nmol)	TNF (pg ml^{-1})	NO (mnol)	Bacterial growth (CO_2)	Survival rate (%)
Amputation	7(3)	0·93(0·1)	2·6(0·7)	267(24)	218(4)	95
Amputation plus GM–CSF	21(4)*	1·4(0)*	5·2(0·6)*	175(8)*	194(6)*	35

Values are mean(s.e.m.). *$P < 0{\cdot}05$ (unpaired *t* test)

Administration of GM–CSF after injury was protective against systemic bacterial proliferation and the development of lethal sepsis. The mechanisms of action appear to include stimulation of neutrophil influx into the peritoneal cavity and priming of peritoneal macrophages for enhanced antimicrobial defence (O_2^-, TNF), with a decrease in the immunosuppressive factor NO. These findings identify novel mechanisms of action of GM–CSF in the injured state and indicate a potential role for this cytokine in the traumatized host predisposed to infection.

Murine acute pancreatitis is associated with decreased interleukin 2 production, susceptibility to sepsis and improved survival with recombinant interleukin 2 therapy

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Blunt trauma and thermal injury in humans are associated with decreased production of interleukin (IL) 2. Murine models of thermal injury have confirmed these findings and immunomodulation with exogenous IL-2 can reverse both immunological abnormalities and susceptibility to mortality from sepsis. Acute pancreatitis is also complicated by sepsis in a large proportion of cases and immunomodulation may be appropriate therapy. It is hypothesized that acute pancreatitis is associated with decreased IL-2 production and that IL-2 therapy can restore immunological competence in the light of a septic challenge.

In the present study acute pancreatitis was induced in adult Swiss–Webster mice by exposure to a choline-deficient ethionine-supplemented (CDE) diet for 10 days. Splenocytes were examined for their ability to produce IL-2 *in vitro*. Animals were challenged with 0·2 mg kg^{-1} endotoxin on day 10 and mortality assessed. Further groups of animals were treated with 15 000 units recombinant IL-2 daily for 5 days and subsequently challenged with endotoxin or had IL-2 production measured on day 10.

Animals fed the CDE diet produced 39 per cent less IL-2 than control mice on day 10 ($P < 0{\cdot}005$) and had 90 per cent mortality rate compared with nil for controls ($P < 0{\cdot}0001$). Treatment with IL-2 significantly improved IL-2 production (1·54 *versus* 0·73 units, $P < 0{\cdot}05$) and survival rate (57 *versus* 0 per cent, $P < 0{\cdot}05$) compared with control animals treated with vehicle only.

It is concluded that recombinant IL-2 therapy is an effective means of immunomodulation in murine acute pancreatitis.

Effects of endotoxin and surgery on bacterial translocation in obstructive jaundice

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Bacterial translocation defines the passage of viable resident bacteria, usually Gram-negative aerobes, from the gastrointestinal tract to normally sterile tissues such as the mesenteric lymph nodes. The authors have previously reported that translocation of *Escherichia coli* can occur spontaneously in jaundiced rats. To define this potential mechanism of sepsis in jaundice better, the influence of both operative trauma and endotoxin challenge was investigated.

Sprague–Dawley rats underwent laparotomy and division of the bile duct ($n = 44$) or sham ligation ($n = 32$). At 1 week, animals from each group were subjected to one of the following challenges: operative trauma (bowel handling for 3 min); *E. coli* endotoxin (lipopolysaccharide: LPS) 0·3 mg kg^{-1} intravenously; or saline intravenously. After 24 h, the rats were killed and the mesenteric lymph node complex excised and cultured for *E. coli* using standard bacteriological techniques.

	Incidence of translocation		
	Saline	Surgery	LPS
Sham ligated	0 of 10	4 of 12	4 of 10
Bile duct ligated	8 of 12	10 of 18	13 of 14*

*$P < 0{\cdot}001$ *versus* saline-treated bile duct ligated group and $P < 0{\cdot}05$ *versus* sham ligated group

Biliary obstruction promotes translocation of *E. coli*, and this process is significantly enhanced by *E. coli* endotoxin challenge, but not by operative trauma. These data suggest a mechanism of sepsis in obstructive jaundice whereby translocation of *E. coli* may itself perpetuate a cycle of bacterial translocation.

Dietary fish oil improves myocardial responsiveness to adrenergic stimulation *in vitro* in the endotoxic rat

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During Gram-negative sepsis there is myocardial depression believed to be mediated by the release of endotoxin. Dietary fish oils have attracted considerable interest in this context because their constituent ω-3 lipid fraction can modulate the release of cytokines and prostaglandins.

A total of 52 Sprague–Dawley rats were fed 20 per cent beef tallow (saturated lipid) or 20 per cent fish oil for a period of 5 weeks after which they were infused with either 1 mg kg^{-1} endotoxin or saline control over 24 h. The animals were then killed and the force of contraction of the atrial heart muscle measured in response to the β_1-agonist isoprenaline in an *in vitro* organ bath. Data were analysed using curve-fit techniques to find the maximum response and the dose of isoprenaline inducing half-maximum response (EC_{50}).

Endotoxin induced myocardial depression as illustrated by a leftwards shift in the dose–response curves (increased mean(s.e.m.) EC_{50}) in both endotoxin-treated groups (3·38(0·46) and 3·52(0·58) μg *versus* 1·79(0·35) and 1·73(0·42) μg; $P = 0{\cdot}0058$ endotoxin *versus* saline, two-way ANOVA). In addition there was a significant increase in the maximum response to β_1-stimulation in the animals fed fish oil

(0·46(0·05) and 0·50(0·04) g *versus* 0·40(0·04) and 0·37(0·04) g; $P = 0{\cdot}042$ fish oil *versus* beef tallow, two-way ANOVA). The data suggest that a fish oil diet may be useful in the treatment or prophylaxis of septic shock where reduced responsiveness to β_1-adrenergic stimulation is a factor.

Position-dependent neutrophil activation in venous disease

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The production of oxygen free radicals by neutrophils was studied in nine normal legs, 15 legs with venous ulceration and seven legs showing lipodermatosclerosis (LDS) only. Ethical approval was obtained. Blood was obtained from the cephalic vein at rest and from a tributary of the long saphenous vein at the ankle after 5 min with the leg supine preceded by 30 min of leg dependency. Neutrophils were isolated and their maximal oxygen free radical production to the chemotactic peptide f-Met-Leu-Phe determined using luminol chemiluminescence. Results were expressed as the ratio of luminescent counts in the leg to those in the arm.

	Ulceration ($n = 15$)	LDS ($n = 7$)	Controls ($n = 9$)
Luminescence ratio	1·99(0·37)*	1·53(0·02)*	0·91(0·09)

Values are mean(s.e.m.). *$P < 0{\cdot}01$ *versus* controls (Mann–Whitney *U* test)

These results demonstrate activation of neutrophils in the legs of patients with venous hypertension.

Positional changes were subsequently studied in a further seven limbs with venous hypertension. Venepuncture was performed in the supine position at 0 and 30 min. The legs were then allowed to be dependent for a further 30 min and blood was taken 5 min after resuming a supine posture.

	Time (min)		Dependency plus re-elevation
	0	30	
Luminescence ratio	1·51(0·25)	1·48(0·18)	2·85(0·70)*

Values are mean(s.e.m.). *$P < 0{\cdot}05$ *versus* 0 and 30 min (Wilcoxon signed rank test)

Neutrophil activation in venous hypertension is position dependent and may be involved in the aetiology of venous ulceration.

Neutrophil calcium-dependent signal amplification in venous hypertension

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Neutrophil activation may occur by both calcium dependent and independent pathways. The activation of neutrophils in venous hypertension was investigated. Neutrophils extracted from arm and leg venous samples from 20 patients with venous hypertension and nine controls were stimulated with phorbol myristate acetate (PMA) and the chemotactic peptide f-Met-Leu-Phe (FMLP). Ethical approval was obtained. Neutrophil oxidase production was measured by chemiluminescence and expressed as the ratio of counts in the leg to those in the arm.

	Luminescence ratio	
Stimulant	Venous hypertension ($n = 20$)	Controls ($n = 9$)
PMA	1·16(0·08)	1·01(0·10)
FMLP	1·86(0·29)	0·91(0·09)

Values are mean(s.e.m.)

There was no difference between ratios when stimulated by PMA but the ratio was significantly greater in patients with venous hypertension after FMLP stimulation ($P < 0{\cdot}01$, Mann–Whitney *U* test), a finding consistent with calcium-dependent activation.

There was more intracellular calcium released by neutrophils from the leg than by those from the arm (mean(s.e.m.) 46(23) *versus* 13(3) per cent of cell surface area) on FMLP stimulation. Neutrophils from the legs of patients with venous hypertension had significantly fewer FMLP receptors than those from the arm (27·5(9·3) *versus* 39·1(10·2) mean fluorescence units; $P < 0{\cdot}01$, paired *t* test), demonstrating amplification of the signal pathway.

Neutrophil activation in venous disease is associated with amplification of the calcium-dependent pathway.

Microangiopathy of the skin in chronic venous insufficiency

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Blood flow in liposclerotic skin of patients with chronic venous insufficiency has been reported to be increased. Laser Doppler fluxmetry was used to assess whether this is due to an increase in speed of flow or volume of blood cells in the skin.

Fifteen patients with clinical lipodermatosclerosis (LDS) caused by proven chronic venous insufficiency as demonstrated by colour duplex scanning and 15 control subjects were studied supine in an environmental chamber at 22°C. A computer data-logging system recorded laser Doppler flux, blood cell velocity and concentration of moving blood cells from the fluxmeter.

	Flux (units)	Velocity (units)	Concentration (units)
Controls*	33 (22–41)	21 (11–26)	3 (2–5)
Patients with LDS*	50 (38–60)	9 (4–17)	7 (3–13)
Median difference (95% confidence interval)	18 (9–32)	8 (2–16)	3·5 (0·1–8)
P†	<0·001	0·01	0·03

*Values are median (interquartile range). †Mann–Whitney *U* test

These results indicate that a higher flux in liposclerotic compared with normal skin was caused by a higher proportion of moving red blood cells in the skin. The cell velocity was greater in normal skin. This finding is consistent with the suggestion that capillaries in liposclerotic skin are dilated and engorged with sluggishly moving blood cells.

Smoking-induced changes in saphenous vein: morphology and release of endothelium-derived relaxing factor

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Smoking is associated with a decreased patency of femoropopliteal vein grafts. It may both promote thrombosis and effect intrinsic changes in saphenous vein. Endothelium-derived relaxing factor (EDRF), which effects vasorelaxation and inhibits platelet aggregation, could be important to graft survival.

Proximal saphenous vein was obtained at varicose vein and bypass surgery. Smoking status was validated by serum cotinine analysis. Specimens were prepared for electron microscopy and vein rings for organ-bath studies.

Transmission electron micrographs distinguished two groups of varicose veins with normal basal lamina ($n = 6$) and with thickened basal lamina ($n = 6$). The former group were all from non-smokers and the latter all from heavy smokers. Thickened basal lamina was also observed in the veins of smokers used for bypass. Immunogold labelling studies demonstrated similar permeability to albumin in all specimens.

All vein rings relaxed (90–100 per cent) in response to nitroprusside. The mean(s.e.m.) maximum bradykinin-induced relaxation was 50·0(5·3) per cent in non-smokers ($n = 7$) compared with 31·6(2·2) per cent in smokers ($n = 9$) ($P = 0{\cdot}03$); preincubation of the smokers' veins with EDRF precursor (3 mmol l^{-1} L-arginine) did not increase the relaxation. Similarly, mean(s.e.m.) maximum relaxation induced by the calcium ionophore A23187 was 53·3(4·3) per cent in non-smokers ($n = 4$) compared with 39·5(4·3) per cent in smokers ($n = 4$) ($P = 0{\cdot}1$).

Smoking appears both to inhibit EDRF release and cause thickening of the basal lamina in saphenous vein. Such changes could contribute to the poorer outcome of vascular reconstruction in smokers.

Effect of intermittent pneumatic foot compression on the microcirculation in arterial disease relaxing factor

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The venous pump of the foot assists blood returning to the heart. The aim of this study was to evaluate the effect of mechanical activation of the foot pump on the microcirculation in patients with peripheral occlusive arterial disease. Fifteen patients with this condition (ankle:brachial pressure index <0·7) and 15 control subjects were studied. The studies were carried out in an environmental chamber at 22°C. After an acclimatization period of 20 min, a pneumatic foot pump (AV Impulse System; Novamedix) was applied to the foot. Laser Doppler flux and transcutaneous oxygen tension (P_{tcO_2}) were measured on the great toe with the subject supine before and during a 10-min foot-pumping period. The study was repeated with the subject sitting.

	P_{tcO_2} (mmHg)		Flux (units)	
Subject sitting	Patients	Controls	Patients	Controls
No pump*	53 (50–60)	58 (46–68)	50 (45–50)	70 (40–100)
Pump on*	62 (54–70)	62 (50–74)	130 (90–200)	150 (100–300)
Increase (%)	8	10	57	66
Median difference (95% confidence interval)	6 (4–10)	6·5 (4–9)	82 (60–130)	124 (73–175)
P†	<0·01	<0·01	<0·001	<0·001

*Values are median (interquartile range). †Wilcoxon matched pairs test

The results confirm that application of the foot pump in the sitting position resulted in an increase in flux and P_{tcO_2} in patients with arterial disease and control subjects. In the horizontal position, foot pumping produced no significant effects.

Familial abdominal aortic aneurysm: prevalence and the role of screening

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Ultrasonographic screening for abdominal aortic aneurysm (AAA) in men over the age of 65 years has become well established. The apparent familial tendency towards AAA suggests that relatives of patients with aneurysm may form a further subpopulation in whom screening is appropriate.

First-degree relatives of 100 consecutive patients with aneurysm were identified. Of 110 relatives over 50 years of age, two were known to have had AAA and 74 had undergone ultrasonography, providing information on aortic size for 76 relatives (69 per cent). Nine relatives were demonstrated to have aortic dilatation (anteroposterior diameter 2·5–3·9 cm) although no further aneurysms (diameter ⩾4·0 cm) were found on scanning.

Aortic dilatation or aneurysm was observed in 24 per cent of male first-degree relatives over 50 years of age, affecting 26 per cent of sons and 22 per cent of brothers. This is a higher prevalence than seen in the general male population and appears to be independent of other vascular risk factors such as smoking, cholesterol levels, hypertension and peripheral vascular disease (all P not significant). Only 7 per cent of sisters and none of the daughters were found to have aortic enlargement.

The prevalence of aortic enlargement is sufficiently high among male first-degree relatives over 50 years of age to justify screening.

Subintimal angioplasty of femoropopliteal artery occlusion: long-term results

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The novel technique of subintimal angioplasty has been attempted on 200 consecutive femoropopliteal artery occlusions of median length 11 (range 2–37) cm. The principle of the technique is to traverse the occlusion in the subintimal plane, exit immediately distal to the occlusion, and recanalize by inflating the angioplasty balloon within the subintimal space.

The technical success rate was 159 of 200 (80 per cent) and was not significantly different for occlusions ⩽10 cm (81 per cent, $n = 73$), 11–20 cm (83 per cent, $n = 63$) or >20 cm (68 per cent, $n = 23$) in length ($P = 0{\cdot}20$). There were no deaths or limb losses resulting from the procedure. The median (range) ankle:brachial pressure index increased from 0·61 (0·21–1·0) before angioplasty to 0·90 (0·26–1·50) after. The actuarial haemodynamic patency rates at 12 and 48 months were 71 and 41 per cent respectively; the symptomatic patency rates were 73 and 51 per cent. Multiple regression analysis using the Cox proportional hazards method showed that smoking multiplied the risk of occlusion by 2·70 ($P < 0{\cdot}001$), each additional run-off vessel reduced the risk by 0·54 ($P < 0{\cdot}001$) and the risk increased by 1·73 ($P = 0{\cdot}02$) for every 10 cm of occlusion.

In conclusion, the technical success rate of subintimal angioplasty for femoropopliteal occlusion is unrelated to occlusion length and excellent long-term cumulative symptomatic and haemodynamic patency rates can be achieved. The factors influencing patency at 4 years were smoking, the number of calf run-off vessels and occlusion length.

Non-invasive measurement of renal blood flow: comparison with radiolabelled microspheres

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Fractionation is the basis on which cardiac output and organ blood flow are measured simultaneously using radiolabelled microspheres. The technique is widely used in haemodynamic research but is too invasive for clinical research. However, the principle may be extended to measure renal blood flow using dynamic scintigraphy and the aim of the present study was to compare the scintigraphic technique with radiolabelled microspheres in the measurement of renal blood flow.

Four groups of ten Wistar rats received intraventricular or intravenous injection of pertechnetate or Mag3 (a renal tubular agent). Immediately after scintigraphy labelled microspheres were injected via the left ventricle to determine cardiac output and renal blood flow.

There was a significant correlation between renal blood flow determined by microspheres and by either intraventricular or intravenous pertechnetate ($r = 0{\cdot}99$, $P < 0{\cdot}0001$; $r = 0{\cdot}80$, $P < 0{\cdot}005$ respectively). There was a similar correlation when Mag3 was used by either route ($r = 0{\cdot}95$, $P < 0{\cdot}0001$; $r = 0{\cdot}99$, $P < 0{\cdot}0001$ respectively). The mean difference between the techniques ranged from 0·07 to 0·63 per cent of cardiac output.

The results confirm that there is close agreement between the pertechnetate and Mag3 fractionation and microsphere methods in measuring renal blood flow. The non-invasive nature of the scintigraphic technique allows it to be used in clinical practice.

Diabetes does not influence the clinical outcome of operative lumbar sympathectomy for severe non-reconstructible peripheral vascular disease

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Lumbar sympathectomy is likely to be less effective at relieving peripheral vascular disease (PVD) in diabetic patients than non-diabetics because of autonomic neuropathy. To determine whether this is the case, the clinical success (resolution of rest pain or trophic foot changes) or failure (periknee amputation) of operative lumbar sympathectomy for severe non-reconstructible PVD (rest pain and/or trophic changes) performed in 44 diabetic and 55 non-diabetic patients was compared. The two groups were matched for age (mean 73 years) and sex ratio (M:F 2:1). Histological analysis confirmed sympathetic ganglia in all patients. No difference was found in the morbidity and mortality rates in the two groups. Five diabetic and eight non-diabetic patients who died within 3 months of sympathectomy were excluded from analysis; the remainder were followed for 6–48 months. After sympathectomy, rest pain was relieved in 15 diabetic and 26 non-diabetic patients ($\chi^2 = 3{\cdot}4$, $P = 0{\cdot}06$); trophic foot changes resolved in 16 and 26 respectively ($\chi^2 = 2{\cdot}7$, $P = 0{\cdot}10$). Periknee amputation was performed in 23 diabetic and 21 non-diabetic patients ($\chi^2 = 1{\cdot}7$, $P = 1{\cdot}9$) at a similar rate after operation (66 per cent within 6 months, $P = 0{\cdot}11$). In conclusion, diabetes influences neither the success nor failure of lumbar sympathectomy for non-reconstructible PVD.

Announcements

Rhone–Poulenc Rorer Surgical Trainees Travel Award 1993

The Rhone–Poulenc Rorer Travel Award for Surgeons in Training is arranged for the Association of Surgeons in Training (ASIT) and the British Orthopaedic Trainees Association (BOTA). It is aimed to promote the exchange of information from surgical specialties across the international community.

A first prize of £1500 will be awarded to the trainee who, in the opinion of the judges, has written the most outstanding dissertation on any aspect of surgical oncology. A second prize of £750 will also be awarded.

This award is open to all trainees who are members of either ASIT, BOTA or the Irish Senior Registrars Group in Surgery.

The closing date for entry is 31 July 1993.

Davis and Geck ASIT Travelling Scholarships

These Scholarships have been created to assist in the cross-fertilization of ideas, skills and surgical techniques within the international surgical community. The Scholarships are open to all ASIT members and two winning candidates will receive either £1000 or £500 towards their costs. The recipients will be announced in September at the ASIT AGM. The Scholarships are not aimed at assisting papers to be read abroad but are to help members in gaining clinical experience by direct contact with surgeons overseas.

Applications (approximately 250 words) must include the proposed itinerary, purpose of visit and probable cost, and a letter of acceptance from the centre(s) to be visited. Application forms are obtainable from your local Davis and Geck representative or Bob Baigrie, Secretary of ASIT, 7 Coverley Road, Oxford OX3 7ET.

Applications must be in the hands of the Secretary by 31 August 1993.

R. J. Baigrie
Honorary Secretary
Association of Surgeons in Training

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, May, 668–669

A selection from the April issue of the American journal.

Changes in energy substrates in relation to arterial ketone body ratio after human orthotopic liver transplantation

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Background. *Changes in energy substrate metabolism, as well as those in arterial ketone body ratio (KBR; acetoacetate/3-hydroxybutyrate), were investigated to follow energy status of hepatic allograft.*
Methods. *Plasma concentrations of energy substrates were measured immediately after 35 orthotopic liver transplantations in 32 adult patients.*
Results. *Twenty-three patients left the intensive care unit within 1 month (group A), six patients were forced to stay in the intensive care unit longer than 1 month (group B), and the other six grafts failed within 1 month (group C). In group B the KBR was significantly lower than in group A 6 hours after reperfusion of the grafts (0.70 ± 0.09 vs 1.21 ± 0.10, mean ± SEM; $p < 0.05$). In group C the KBR remained significantly lower than in group A at 6 hours (0.65 ± 0.04 vs 1.21 ± 0.10; $p < 0.01$), on the first postoperative day (0.64 ± 0.03 vs 1.36 ± 0.10; $p < 0.001$), and on the second postoperative day (0.65 ± 0.02 vs 1.58 ± 0.11; $p < 0.01$). Total ketone body concentration (TKB) was significantly higher in group B than in group A at 4 hours (462.9 ± 105.0 µmol/L vs 201.6 ± 32.6 µmol/L; $p < 0.001$), 6 hours (483.4 ± 102.1 µmol/L vs 125.5 ± 25.9 µmol/L; $p < 0.001$), and the first postoperative day (481.1 ± 196.6 µmol/L vs 123.9 ± 24.1 µmol/L; $p < 0.001$). No increase in TKB was observed in group C.*
Conclusions. *It is suggested that low values in KBR accompanied with low levels of TKB should be regarded as a strong indicator of graft failure and fatty acid oxidation and ketogenic pathways are accelerated to compensate for energy deficits in patients with low values in KBR and high levels of TKB until KBR recovers immediately after orthotopic liver transplantation. (*Surgery *1993;113:403-9.)*

Peritoneovenous shunting of intractable ascites in patients with cirrhosis: Improving results and predictive factors of failure

Sophie Hillaire, MD, Michele Labianca, PhD, Giacomo Borgonovo, MD, Claude Smadja, MD, PhD, Didier Grange, MD, *and* **Dominique Franco, MD,** *Clamart and Evry, France*

Background. *The clinical results of peritoneovenous shunting have not been entirely satisfactory in spite of dramatic improvement of renal function and decrease of ascites. The purpose of this study is to determine whether certain modifications improved our results.*
Methods. *A modified LeVeen shunt was electively inserted in 56 patients who had cirrhosis with intractable ascites. In 24 patients (42.9%) the Child-Pugh's score was less than 9, and in 32 patients the score was 9 or above. Fourteen patients (25%) had previous variceal bleeding, and 15 patients (26.8%) had previous spontaneous bacterial peritonitis (SBP). LeVeen shunt was modified by the addition of a titanium venous catheter tip. Prophylactic antibiotic therapy was administered to all patients.*
Results. *No operative deaths occurred, and one patient had severe postshunt coagulopathy. Five patients (8.9%) experienced recurrent ascites resulting from blockage of the shunt. The cumulative rate of shunt blockage was 5.6% at 1 year and 12% at 2 years. Seventeen patients (30.3%) have recently had variceal bleeding. The cumulative risk of variceal bleeding was significantly higher in patients with a previous hemorrhage than in those patients without ($p < 0.05$). Eight patients (14.3%) had SBP after operation. The cumulative risk of SBP was higher in patients with a history of SBP than in those patients without, although the difference was not significant. Fifty-five percent of late deaths were related to variceal bleeding or to SBP. Overall cumulative 1- and 2-year survival rates were 67.2% and 55.2%, respectively. It was 82% and 71% in patients without previous variceal bleeding or SBP.*
Conclusions. *These data suggest that peritoneovenous shunting might be beneficial only in selected patients. Previous variceal bleeding and/or SBP indicate liver transplantation in suitable patients. (*Surgery *1993;113:373-9.)*

A gastroplasty that avoids stapling in continuity

L. D. MacLean, MD, FRCS(C), FACS, B. M. Rhode, PDt, MSc (Nutr), CNSD, *and* **R. A. Forse, MDCM, FRCS(C), FACS,** *Montreal, Quebec, Canada*

Background. *Staple line perforations have been the principal cause of failure after vertical-banded gastroplasty in patients followed at least 4 years at our institution. In the present study an operation was devised that created a vertical-banded gastroplasty not dependent on staple lines to avoid this complication.*
Methods. *One hundred two patients with a body mass index (BMI) greater than 35 kg/m^2 underwent vertical-banded gastroplasty from Jan. 1 to Dec. 30, 1986, with an orifice size of 45 to 47 mm external circumference and division between the vertical staple lines to prevent gastric pouch to gastric fundus fistula.*
Results. *Ninety-eight of the patients have been followed up for a minimum of 4 years. Sixty-two percent of patients obtained an excellent or good final result after 4.5 ± 0.1 years. This was*

a BMI of less than 35 kg/m^2 or less than 50% excess weight. This acceptable long-term result was achieved 90% of the time if the patient was obese (BMI, 35 to 40 kg/m^2) before surgery and in 75% of patients who were morbidly obese (BMI, 40 to 50 kg/m^2) but in only 30% of patients who were superobese (BMI > 50 kg/m^2) before surgery. Staple line disruption was markedly reduced; however, stenosis or failure to lose weight or late weight gain required reoperation in 36% of the patients.

Conclusions. *Gastric bypass was superior to reversal or revision of the gastroplasty as a remedial operation. This study again questions the value of vertical-banded gastroplasty in the treatment of obesity even when staple line disruption is markedly diminished. (*SURGERY *1993;113:380-8.)*

Donor hepatectomy for living related partial liver transplantation

Masatoshi Makuuchi, MD, Seiji Kawasaki, MD,
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Hidetoshi Matsunami, MD, Ken Hayashi, MD,
Haruhisa Harada, MD, Tohru Kakazu, MD,
Tadatoshi Takayama, MD, *and* **Hideo Kawarasaki, MD,**
Matsumoto and Tokyo, Japan

Background. *An essential prerequisite for living related partial liver transplantation is to perform donor hepatectomy with minimal risk while preserving graft viability. This article describes a safe method of donor hepatectomy that was used for five patients who underwent living related liver transplantation.*

Methods. *Liver parenchymal transection was performed by the selective vascular occlusion technique in four patients, and interruption of the blood supply to the left medial segment was carried out along the right side of the umbilical portion before parenchymal division in the other patient.*

Results. *These procedures resulted in insignificant intraoperative blood loss, for which no banked blood or blood derivatives were transfused. The postoperative course for each of the five donors was uneventful, and excellent graft viability was verified by the fact that the five recipients showed a good immediate postoperative course without marked increases in the serum activities of liver enzymes.*

Conclusions. *We believe that the operative risk of living related donor hepatectomy is minimal if it is performed by experienced liver surgeons with the present procedures. (*SURGERY *1993;113:395-402.)*

Management of arterial injuries produced by percutaneous femoral procedures

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Sushil K. Gupta, MD, *and* **Kurt R. Wengerter, MD,**
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Background. *A significant number of vascular injuries occur with the use of percutaneous diagnostic and therapeutic procedures. This study was done to indicate the types of these injuries and their management.*

Methods. *Over a 30-month period, 55 patients required operation for vascular complications after percutaneous femoral procedures including infrarenal arteriography (six patients) and angioplasty (22 patients), coronary angiography (16 patients) and angioplasty (five patients), and aortic balloon pump insertion (six patients).*

Results. *The 14 iliac and 41 femoral artery injuries included 29 pseudoaneurysms, six lacerations with persistent bleeding, seven dissections, six occlusions, three ruptures, two arteriovenous fistulas, and two large hematomas. Control for all femoral and distal external iliac artery lesions was obtained solely through a groin incision in 45 (82%) patients. Our technique for exposure of the external iliac artery through the groin is described. A separate retroperitoneal incision was necessary in 10 patients because of proximal injury, massive pseudoaneurysm, morbid obesity, or heavily scarred groins. In this series 34 lateral suture repairs, 11 interposition or bypass grafts, four patch angioplasties, one endarterectomy, three thrombectomies, and two hematoma evacuations were performed. Although no limb loss occurred, we encountered nine wound complications, five myocardial infarctions, and two deaths.*

Conclusions. *This experience shows the wide variety of vascular complications caused by percutaneous procedures and the different techniques necessary for their management. (*SURGERY *1993;113:419-25.)*

Hormone secretion by normal human parathyroid cells in vitro: Characterization by the reverse hemolytic plaque assay

Miguel F. Herrera, MD, Clive S. Grant, MD, FACS,
Peter Maercklein, MS, Jon A. van Heerden, MB,
FACS, FRCSC, *and* **Lorraine A. Fitzpatrick, MD,**
FACP, *Rochester, Minn.*

*We have recently validated a reverse hemolytic plaque assay (RHPA) for the quantitative measurement of parathyroid hormone release from single isolated parathyroid cells. The information regarding secretory behavior of normal and abnormal parathyroid tissue has been based previously on fluorescent spectroscopy or quantification of immunoreactive parathyroid hormone by radioimmunoassay. Thus, individual differences in secretion and assessment of viability are not clearly measured in these types of experiments. The RHPA has the advantage of allowing measurements of secretory activity in individual viable parathyroid cells. In this report, we have modified the RHPA to measure the release of parathyroid hormone from human cells. This is the first instance of measurement of hormone secretion from human cells, and we present data indicating the specificity of the assay for human parathyroid hormone. The response of normal human parathyroid cells to alterations in extracellular calcium was assessed by two parameters: the ability of an individual cell to secrete parathyroid hormone in response to a stimulus and the recruitment of normal human cells to release parathyroid hormone. This assay will allow elucidation of secretory dynamics in normal and abnormal glands, which may help us to understand the mechanisms involved in parathyroid dysfunction. (*SURGERY *1993;113:410-8.)*

Correspondence

Timing of surgery for breast cancer in relation to the menstrual cycle and survival of premenopausal women

Sir

The recent publications by Mr Nathan and colleagues (*Br J Surg* 1993; **80**: 43) and Gnant *et al.*[1] outlining their results on the timing of surgery within the menstrual cycle and the outcome of patients with breast cancer again highlight the controversy over this subject. Both groups report finding no effect, in contrast to the studies of Badwe *et al.*[2] who found an increased mortality rate for those operated on in days 3–12 of the cycle. The results from Yorkshire[3] showed an opposite result with an improved survival for those operated on in the first half of the cycle.

To investigate this subject further, we have set up a multicentre prospective study and invite interested groups to join us. In addition to collecting data on the timing of operation and other interventions such as mammography or cytology, the regularity of cycle, and duration and type of contraceptive pill use will also be recorded. Blood samples will be taken for oestrogen, progesterone, luteinizing hormone and follicle-stimulating hormone analysis to relate hormonal findings to any observed effects. Copies of the protocol along with samples of the data collection forms can be obtained from the Clinical Trials Unit at the Yorkshire Regional Cancer Organisation (Tel. 0532 300566), through which the study is being coordinated. Anyone with an interest in the management of premenopausal breast cancer is encouraged to join the study.

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Pneumothorax during laparoscopic dissection of the diaphragmatic hiatus

Sir

We write to bring attention to the risk of pneumothorax during laparoscopic dissection of the diaphragmatic hiatus. We have recently observed this in two patients, one undergoing laparoscopic hiatus hernia repair and the other laparoscopic Heller's cardiomyotomy and fundoplication for achalasia of the cardia.

A 39-year-old woman with a 10-year history of reflux oesophagitis underwent laparoscopic hiatus hernia repair. During dissection of the diaphragmatic hiatus to mobilize the oesophagus a left pneumothorax caused a sudden fall in oxygen saturation (measured by pulse oximetry from 97 to 41 per cent). Chest radiography confirmed a left pneumothorax. The laparoscopic procedure was converted to an open operation and a chest drain inserted into the pleural cavity. The drain was removed the following day and the patient made a full recovery.

A 45-year-old man with achalasia of the cardia underwent laparoscopic Heller's cardiomyotomy. The hiatus was dissected to mobilize the oesophagus for 10 cm above the oesophagogastric junction. A long cardiomyotomy was performed laparoscopically, extending several centimetres down on to the stomach. A Nissen-type fundoplication was attempted to prevent gastric acid reflux, but the patient suddenly developed transient hypotension (blood pressure 64/40 mmHg) and oxygen saturation fell from 97 to 92 per cent; ventilation pressures rose. After fundoplication was completed chest radiography confirmed a left pneumothorax and surgical emphysema was present in the neck and chest wall. A chest drain was inserted with rapid improvement of the patient's condition. The drain was removed the following day and the patient made a full recovery.

Pneumothorax has been reported following straightforward diagnostic laparoscopy and laparoscopic cholecystectomy. It is thought to be caused by a congenital defect of the diaphragm (patent pleuroperitoneal canal), through which the insufflated gas passes into the thoracic cavity[1,2]. Both of the patients presented developed a left pneumothorax following hiatal dissection, presumably resulting from inadvertent damage to the pleura. Neither had a history of respiratory disease. The fall in oxygen saturation in the first patient and the fall in blood pressure and oxygen saturation with increase in ventilation pressure in the second brought the situation to the anaesthetist's attention. However, clinical observation of reduced chest expansion and diminished breath sounds on auscultation were present in each case. The increased peritoneal cavity pressure, maintained automatically at about 15 mmHg by carbon dioxide insufflation, may heighten the risk of a tension pneumothorax. We now believe that when pneumothorax is suspected the pneumoperitoneum should be deflated until the diagnosis is confirmed radiographically and a chest drain is inserted. Awareness of the risk and a high index of suspicion of pneumothorax are needed during laparoscopic surgery at the diaphragmatic hiatus. Care in dissection is essential. However, the presence of a pneumothorax need not result in conversion to an open procedure.

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Lasers in surgery

Sir

We read with interest the Review by Messrs Murray, Mitchell and Wood (*Br J Surg* 1992; **79**: 21–6). While it gave an accurate account of lasers currently available, it reported inaccurately that the argon laser (wavelength 488/514 nm) is used in the treatment of port wine stains. Such lesions are presently treated successfully with the flashlamp-pulsed tunable dye laser (wavelength 585 nm). Since the first published report[1] of its successful use in the treatment of port wine stains in 1989, this laser has been shown to be far superior to the argon laser in the treatment of port wine stains and has not been associated with the hypopigmentation and hypertrophic scarring found with the latter[2].

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Prevalence of abdominal aortic aneurysm in the offspring of patients dying from aneurysm rupture

Sir

We welcomed the paper by Drs Bengtsson *et al.* (*Br J Surg* 1992; **79**: 1142–3) reporting the prevalence of abdominal aortic aneurysm (AAA) in the offspring of Swedish patients who had died from ruptured aneurysm. Allowing for the differences in the definition of AAA, their results are similar to those in our own study of English subjects that were presented to the Surgical Research Society in January 1993 and are published in abstract form in the present issue[1]. In this study we invited 110 first-degree relatives (over 50 years of age) of 100 consecutive patients with AAA to undergo ultrasonographic examination of the aorta. Maximum anteroposterior aortic diameter was measured and the aorta classed as either normal (<2·5 cm), enlarged 2·5–3·9 cm) or aneurysmal (≥4·0 cm) in accordance with our local screening practice. Two relatives had previously been known to have AAA and 74 (67 per cent) underwent scanning. Nine of these had enlarged aortas, although none was aneurysmal. In total, aortic dilatation was observed in five of 23 brothers and four of 15 sons, prevalences that support the findings from both Dr Bengtsson's current paper and their previous work[2].

The natural history of non-aneurysmal aortic enlargement is unclear. Mean annual growth rates of 0·11 cm for infrarenal aortas between 2·5 and 2·9 cm in maximum anteroposterior diameter and 0·29 cm for those 3·5–3·9 cm in diameter have previously been reported, with up to 11 per cent enlarging by more than 5 mm per annum[3]. We are scanning our subjects with aortic enlargement at yearly intervals to determine the risk of developing true aneurysmal disease of the abdominal aorta.

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Incidence and prognosis of Krukenberg tumour in Northern Ireland

Sir

I read the article by Messrs Gilliland and Gill in the December issue of the Journal on the incidence and prognosis of Krukenberg tumour (*Br J Surg* 1992; **79**: 1364–6). They state that the incidence of this tumour varies with the definition used. Some authors[1] include all tumours metastatic to the ovary, irrespective of the site of origin. London and Grossman[2] used the eponym Krukenberg tumour of the testis for a patient with metastasis to the testis from carcinoma of the stomach. I expanded the definition to include metastasis to ovaries and testes from known or unknown primary tumours, irrespective of the histological type[3,4]. Thus Krukenberg tumours are metastatic tumours of the gonads of any histological type, from a known or unknown primary site.

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Authors' reply

Sir

Dr Shetty emphasizes in this and his previous two publications[1,2] that the expansion of the definition of the Krukenberg tumour to include any metastatic tumour of the gonads regardless of the primary source or histological type was a personal description. The previous report by London and Grossman[3] of a metastasis of the testis that resembled a Krukenberg tumour was published in 1949 and has subsequently been updated by Woodruff and Novak[4], Hale[5] and the World Health Organization[6].

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1. Shetty MR. Krukenberg tumor of the testis. *Urology* 1989; **33**: 351 (Letter).
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Mechanical properties of the aneurysmal aorta

Sir

I read with interest the paper by Mr MacSweeney and colleagues (*Br J Surg* 1992; **79**: 1281–4) on mechanical properties of the aneurysmal aorta. The methodology and findings are fascinating, but the article seems to be clouded by a fundamental misunderstanding of the concept of tension. Tension in the wall of a cylinder or sphere is that force which tends to distract two points in the wall of such a body. It is not, as the authors seem to suggest, the resistance of the wall opposing such a force. Laplace's law, as quoted, tells us that for a given intraluminal pressure the tension in the wall of a vessel increases in proportion to its radius and in inverse proportion to the thickness of the wall. If we imagined that the vessel wall behaved as a simple elastic structure the strain produced would be proportional to this tension and would, for any increment in pressure, be greater as the vessel became wider and the wall thinner. As the pressure–strain elastic modulus is inversely proportional to strain, it would decrease with such changes and not increase as stated in the article. The mean arterial pressure would produce a tension in the wall, but would not affect the additional tension and hence strain produced by the incremental pressure between diastole and systole. It would not, therefore, affect the elastic modulus.

The point about collagen fibres being recruited to load bearing as elastin fibres are stretched is noted. However, when considering the concept of an elastic modulus, it is worth mentioning that even the simplest materials obey Hooke's law with a linear relationship between stress and strain only within certain limits. If a material is deformed beyond its elastic limit the stress–strain ratio changes, the stretching is no longer reversed on releasing the tension, and breaking-point is eventually reached.

The authors wrongly state in their discussion that the increased wall tension in larger aneurysms would 'resist further distension'. On the contrary, tension is the force that tends to distend and ultimately rupture the aneurysm.

The mechanical properties of the living aortic wall in different healthy and diseased subjects are clearly not simple. The authors make a useful contribution to our understanding but need not make the subject appear more complex than it is by confusing the simpler aspects of physics relevant to interpretation of their data.

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Authors' reply

Sir

We thank Mr Hinson for his letter. For more than a century it has been recognized that the elastic properties of the arterial wall are non-linear[1]. Mr Hinson imagines that the vessel wall behaves as a simple elastic structure. Comments based on this assumption are erroneous and irrelevant.

Our discussion of the elastic properties of arteries emphasized that these are non-linear and that 'the more an artery is stretched the more difficult it becomes to dilate it further'. Consequently one would predict that arteries would be more difficult to stretch, or distend, at higher mean arterial pressure or with increasing diameter. Under these conditions the pressure–strain elastic modulus increases.

We agree that tension is the force tending to distract two points on the circumference of a cylinder. Perhaps the sentence Mr Hinson questions should have been constructed as 'in the dilated aorta the increased wall tension would result in a less elastic aortic wall that would resist further distension'. Nevertheless we believe that, in the context of our discussion, the original meaning was clear.

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1. Roy CS. Elastic properties of the arterial wall. *J Physiol* (*Lond*) 1880; 3: 125–59.

Parotidectomy for parotid tumours: 19-year experience from the Netherlands

Sir

The recent paper by Dr Debets and colleagues (*Br J Surg* 1992; 79: 1159–61) prompts me to write. Although their findings are important, they have overlooked the fact that several previous studies have reached similar conclusions.

We have reviewed the records of 84 patients presenting with a lump in the parotid region over an 8-year period[1,2]. Forty-four patients (34 men) were investigated by fine-needle aspiration cytology (FNAC). The preoperative cytological diagnosis was compared with the final histopathological result after examination of the surgical specimen. Additionally, the last 18 patients underwent computed tomography (CT) of the parotid region. Diagnostic accuracy was 100 per cent with pleomorphic adenoma and 75 per cent with adenolymphoma, with no false-positive or false-negative diagnosis of malignancy. Follow-up ranged from 4 to 96 (mean 30) months and there have been no local recurrences to date.

Subsequently, the morbidity rate following 112 operations on the parotid gland was reviewed. Facial nerve palsy (temporary 38 per cent, permanent 9 per cent) and Frey's syndrome (11 per cent) were common following superficial parotidectomy. A more limited 'lumpectomy' produced only 3 per cent temporary palsy with no permanent lesion. A comparison of complications before and after routine use of FNAC and CT showed that the latter group of patients had a lower morbidity rate ($P < 0.05$, unpaired t test).

The conclusions of these two studies are (1) that formal superficial parotidectomy is justified for pleomorphic adenoma and frank malignancy and (2) that benign and superficial lesions (including adenolymphoma), which can be differentiated safely and accurately by FNAC and CT, should be treated by a more limited surgical procedure, which has a lower complication rate.

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Role of endoscopic retrograde cholangiopancreatography in the investigation of pain after cholecystectomy

Sir

I was delighted by the article from Mr Carlson and colleagues concerning the role of endoscopic retrograde cholangiopancreatography (ERCP) in the investigation of pain after cholecystectomy (*Br J Surg* 1992; 79: 1342–5). ERCP revealed common bile duct stones in 41 per cent of this large group of patients ($n = 384$). It is a common belief that most bile duct stones are symptomless and the cause of pain after cholecystectomy often remains obscure. It would now be very interesting to know the outcome of the patients who had common duct stones removed.

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Authors' reply

Sir

We thank Dr Tuuliranta for his comments. We agree with him that common bile duct (CBD) stones may indeed be present in the absence of symptoms. As indicated our study was retrospective in nature, and we unfortunately do not have any data relating to long-term follow-up of patients in whom stones were removed from the CBD.

It is important to note that the vast majority of patients with calculi had not only abdominal pain but also features indicating that the stones were associated with biliary pathology (abnormal biochemistry in 48 per cent duct, dilatation in 22 per cent and both in 18 per cent). Only 13 per cent of patients had stones in the absence of other features indicative of pathology. We are unaware of any studies that have related common duct stones to symptoms in this group of patients. Furthermore, it would be ethically difficult to justify leaving CBD calculi *in situ* in patients who complained of pain, even in the absence of features suggesting that the stones were associated with duct obstruction.

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Role of sequential leucocyte counts and C-reactive protein measurements in acute appendicitis

Letter 1

Sir

We read with interest the recent article by Mr Thompson and colleagues on diagnostic tests for acute appendicitis (*Br J Surg* 1992; **79**: 822–4). We agree that serial white cell count (WCC) measurement is useful in the clinical diagnosis of acute appendicitis, as has been our experience of 100 consecutive patients recently operated on for right lower quadrant pain. We also agree that 'the total WCC alone is not diagnostic because it has low specificity, although this can be improved by combining the leucocyte count with the differential neutrophil count'.

In our series, the sensitivity and specificity of measuring WCC alone were 70 and 99 per cent respectively. The sensitivity improved to 88 per cent but the specificity dropped to 92 per cent when either the WCC or neutrophil count was raised. Nevertheless, using the criteria quoted in the paper (sensitivity >80 per cent, specificity >90 per cent), the measurements of initial WCC and neutrophil count qualify as diagnostic tests. We do not routinely measure levels of C-reactive protein (CRP) as we think this will not give additional information for clinical decision making but only add to the cost of the admission. We are pleased that this is supported by Mr Thompson and co-workers, who find that CRP measurement 'offers no advantage'.

Although the authors are to be congratulated, there are some issues that raise concern. First, we feel that the use of 11×10^9/l as the sole upper normal limit of total WCC for all patients is inappropriate, as the upper limit varies with age of the patient. In fact, different values have been used for different age groups for analysis[1]. Employing a single cut-off point for the whole group of patients may therefore lead to erroneous calculation of the sensitivity and specificity, whether for the initial or subsequent WCC. However, such an effect is cancelled out in the evaluation of the serial changes in WCC.

Second, our findings suggest that the absolute value of the WCC, but not of the neutrophil count, increases with the severity of inflammation of the appendix. The authors analysed neither the absolute value nor the serial changes of the tests studied in relation to the different grades of appendicitis. It would be of interest to know whether such a relationship exists for the sequential measurements of these parameters.

Third, Thompson *et al.* refer to the operative findings for grading of appendicitis in certain cases, but these may not be totally reliable. For the gangrenous and perforated cases there is hardly an issue. However, it is in that particular and major group of patients with 'inflamed appendix' that descriptions of inflammation differ for different surgeons. For instance, 80 and 9 per cent of cases graded by surgeons as mildly and acutely inflamed appendix respectively were found to be histologically normal[2]. If such is the case in the authors' series, then some of the appendicitis cases should be regarded as normal and should be analysed together with the mesenteric adenitis/non-specific abdominal pain group. This surely would make the interpretation of their results difficult. Perhaps 'a prospective randomized trial to evaluate the use of serial total WCCs in the diagnosis of acute appendicitis' may shed some light in resolving these issues.

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Letter 2

Sir

The findings of Mr Thompson and colleagues (*Br J Surg* 1992; **79**: 822–4) regarding sequential white cell counts in acute appendicitis are interesting. However, the statement that such counts 'fulfil the criteria for a diagnostic test' is perhaps a little misleading since the calculation of specificity was made after retrospectively excluding all patients with diagnoses other than appendicitis and mesenteric adenitis/non-specific abdominal pain (NSAP). More than 11 per cent of the operations revealed other definite diagnoses; a further unspecified number of patients were excluded following clinical recovery without operation. Previous work[1] suggests that some of these will subsequently prove to be harbouring important pathology.

In fact their comparison was between 12 operated patients with mesenteric adenitis/NSAP, of whom 11 were initially prescribed a period of observation before a decision to operate, and 36 patients with appendicitis, of whom only eight presented initial diagnostic problems.

To be clinically useful a diagnostic test is required to distinguish not only appendicitis and mesenteric adenitis/NSAP, but also patients requiring further investigation for conditions whose treatment may be improved by more accurate preoperative diagnosis. Furthermore, while every surgeon strives to reduce the negative appendicectomy rate, a test that achieves this at the expense of delayed or missed diagnosis in even a small number of perforated appendices – not always obvious clinically – may produce little net benefit.

I was also surprised to note that not all their appendix specimens were sent for histological examination. Since qualifying in 1981, I have seen histological reports on apparently 'normal' or 'definitely inflamed' appendices which have revealed diagnoses of carcinoid tumour, *Enterobius vermicularis* infestation (several cases of each) and Crohn's disease apparently confined to the appendix, not to mention several examples of appendicitis and its absence not correctly identified at operation, and a few with histological evidence of inflammation starting on the serosal surface of the organ from another source of sepsis where this had not been recognized at operation. Appendicectomy is frequently performed by inexperienced surgeons. As well as revealing unsuspected diagnoses, routine histological examination of the appendix provides an element of quality control on the decisions of the operating surgeon.

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1. de'Dombal FT, Mathara SS, Staniland JR *et al.* Presentation of cancer to hospital as acute abdominal pain. *Br J Surg* 1980; **67**: 413–16.

Small bowel transit time in patients with intra-abdominal adhesions

Sir

I read with interest the Short Note by Messrs Scott-Coombes, Vipond and Thompson (*Br J Surg* 1992; **79**: 1076), which suggests that small bowel transit in patients with intra-abdominal adhesions may be delayed in the absence of symptoms or clinical evidence of obstruction. They suggest that the lactulose breath hydrogen test may provide a simple non-invasive method for documenting such a delay. The overlap in transit time observed in the two groups of patients and consequent low specificity considerably reduces the effectiveness of the test. However, as no mention was made as to the duration of the test, have the authors considered whether small bowel bacterial overgrowth was responsible for the apparently normal, or even rapid, transit time seen in some of their patients with adhesions? Further prolongation of the test in this group might have resulted in a second peak consistent with the true orocaecal transit time. Hence, the authors may in fact be underselling the potential of measuring small bowel transit time as a means of identifying patients with adhesions.

I would like to add that a non-invasive method for directly measuring contractile patterns in patients with adhesive obstruction confirmed by laparotomy or radiologically has previously been described[1].

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Authors' reply

Sir

Mr Cullen's suggestion that small bowel bacterial overgrowth could account for a falsely low transit time in patients with adhesion was considered. To rule out this possibility, expiratory breath hydrogen samples were measured over a 4-h period in all patients to ensure that a second peak did not occur.

The development of a non-invasive test for intra-abdominal adhesions could lead to the assessment of methods designed to prevent postoperative adhesion formation. The majority of such patients are asymptomatic and, while the study[1] referred to by Mr Cullen successfully identified patients with suspected partial bowel obstruction using surface vibration analysis, all of those patients suffered from 'chronic complaints'. A more sensitive method is therefore required.

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Acute testicular torsion following orchidopexy for undescended testis

Sir

I read with confusion the recent Case Report of acute testicular torsion following orchidopexy for undescended testis (*Br J Surg* 1992; **79**: 1292) by Messrs Hurren and Corder. I agree with the authors that these cases are rare, but am confused by their description of the aetiology as being due to an intact tunica vaginalis, which therefore needs to be everted during the surgical procedure. Since almost all orchidopexies are performed using the 'extravaginal' subdartos pouch, the tunica is bound to remain intact if it has developed at all as the procedure does not interfere with its integrity. Also I am not clear how the tunica can be everted during this procedure since it involves a small incision of not more than 1 cm in the scrotal skin to create the pouch.

The occurrence of testicular torsion following orchidopexy in a subdartos pouch results from one or both of the following technical errors: (1) inadequate or improper creation of the pouch; and (2) formation of a large button hole in the dartos muscle which results in slipping of the testis in the scrotum – as a result, torsion can easily happen. I have operated on two patients who developed testicular torsion in normally developed and descended 'intravaginal' testes for the second time and had already undergone orchidopexy. The reason for the recurrent torsion was the use of two sutures to fix the testis in each case. This manoeuvre resulted in the formation of a long fibrous band, around which the testis had twisted. The appropriate orchidopexy in this circumstance involves the use of four or five stitches on each side of the testis of absorbable material such as polyglactin or polyglycolic acid as non-absorbable material tends to erode through the scrotal skin with time.

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Authors' reply

Sir

We thank Mr Hamad for his comments and hope the following elucidation of the aetiology and operative technique with reference to the embryology clarifies the confusion. The tunica vaginalis of the testis is formed from the processus vaginalis, a pouch of peritoneum that descends with the testicle in the latter stages of gestation[1]. The undescended testis usually lies in the inguinal canal or superficial inguinal pouch invested in its tunica vaginalis. It is the abnormal attachments of this 'intact' tunica vaginalis to the testis that predispose to torsion. The testis is mobilized with its tunica vaginalis through the inguinal incision, and it is at this stage that the tunica vaginalis should be everted. The testis is then brought down (with an everted tunica vaginalis) to a subdartos pouch and the tunica albuginea fixed in the pouch.

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1. Scorer CG. The anatomy of testicular descent – normal and incomplete. *Br J Surg* 1962; **49**: 357–67.

Book reviews

Atlas of Laparoscopic Surgery

E. J. Reddick, W. B. Saye and J. D. Corbitt Jr (eds). 285 × 220 mm. Pp. 116. Illustrated. 1993. New York: Raven Press. US$122·50.

This book is well produced and extensively illustrated with high-quality colour photographs. However, it is disappointing in its range and content. Some 70 of the 116 pages are devoted to a full and clear description of laparoscopic cholecystectomy, with practical instruction on the techniques of safe dissection, cholangiography and laparoscopic bile duct exploration. However, the remaining pages cover a limited range of laparoscopic procedures (appendicectomy, highly selective vagotomy, left colon resection, herniorrhaphy). Other commonly performed procedures that would have been useful to include are hiatus hernia repair and fundoplication, repair of perforated ulcer, right colon resection and bilateral oōphorectomy; mention could have been made of splenectomy, nephrectomy, small bowel resection and colostomy formation.

The description of herniorrhaphy is well written, but the illustrations are slightly confusing in that the side depicted is not stated in any of them, and there is no photograph or diagram to demonstrate the extent of peritoneal dissection. A further minor irritation with this book is the authors' repeated naming of their own instruments and highlighting of one company's disposable equipment throughout the text.

In conclusion, this atlas is good as far as it goes and certainly provides a clear and full description of laparoscopic cholecystectomy. The surgeon who is seeking help with advanced laparoscopic surgery will have to look elsewhere.

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Aberdeen Royal Infirmary – The People's Hospital of the North-East

I. Levack and H. Dudley. 248 × 173 mm. Pp. 274. Illustrated. 1992. London: Baillière Tindall. £17·95.

Although the original initiative for this book came from the bicentennial of the Aberdeen Medico-Chirurgical Club, it is appropriate, at this time of huge changes in the National Health Service, that this historical record of the provision of hospital services in Aberdeen over the past two and a half centuries has recently been published. The overall impression left by this book is of the medical practitioners and people of Aberdeen striving to develop and improve their hospital services. It is to be hoped that this historical perspective will help to ensure that future developments continue in the right direction.

The initial chapters give a general history of the development of the hospital, the evolution of each specialty being dealt with separately in subsequent sections. As a surgeon, I particularly enjoyed the surgical chapter and the description of the reaction to the generous administration of chloroform of a farmer from Glenbucket who was about to undergo an operation for a bladder stone:

> 'After a struggle, requiring his limbs to be steadied by four assistants, and then a good humoured display of Celtic eloquence which lasted for five minutes, he went into a state of complete anaesthesia'.

It is always going to be difficult to compress 250 years of history into a single volume, but the authors have woven fact, comment and illustration together into a fascinating account, which I can recommend to anyone interested in the history of medicine or the North-east of Scotland.

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Surgical Attending Rounds

K. Francis Lee and C. M. Dyke (eds). 278 × 215 mm. Pp. 393. Illustrated. 1992. Philadelphia, Pennsylvania: Lea and Febiger. £21.

This paperback book consists of a series of hypothetical surgical cases briefly presented as on an attending or consultant surgical ward round. Each case forms the basis of a chapter and covers a major topic in general surgery. The questions and answers that follow usually make a good summary of the condition, be it breast cancer, aortic aneurysm or inflammatory bowel disease. The level of knowledge covered is appropriate for final year students and junior surgical staff, and should be helpful both in revision and practice for viva examinations.

There are 32 chapters covering most of general surgery, including burns and renal transplantation, but excluding cardiac surgery, orthopaedics and urology. In the main the questions and answers are skilfully constructed to form a reasonably comprehensive account of the subject and each topic is summarized at the end of the chapter, particularly useful for quick revision. Ten to 20 references are quoted, almost all American, at the end of each chapter.

The authors, mainly residents from the Medical College of Richmond, Virginia, are to be congratulated on the high and uniform standard of presentation. The practice of surgery described differs little from that in a British teaching hospital, although the UK reader will find some difficulty with the method of expressing results, and the relative overinvestigation compared with UK practice. As expected, there is a good deal of Americanese that will grate on some: 'Mr McDonald was placed on NPO, hydrated intravenous, and given antibiotics'.

The book is a valuable adjunct to a standard text, easy to read, and offers good revision material for final year students and house officers.

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Handbook of Total Parenteral Nutrition. 2nd ed.

J. P. Grant. 267 × 185 mm. Pp. 368. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US$35.

This is an excellent single-author textbook outlining the complex problems associated with total parenteral nutrition; this is now an essential part of modern clinical practice and is particularly relevant to any surgeon performing major surgery, especially that of the gastrointestinal tract. John Grant is an Associate Professor of Surgery and Director of the Nutritional Support Service at Duke University Medical Center in North Carolina. He is one of the pioneers of intravenous nutritional support and the strength of this book lies in his personal experience as director of a well established 'nutrition team'.

Grant clarifies the benefits of a nutrition team, outlines the many methods used in the measurement of nutritional status and succinctly comments on their inaccuracies. The reference lists at the end of each chapter are extensive but have tended to ignore the British and European literature. An example is the omission of the excellent central venous catheter tunnelling technique described by Jeremy Powell-Tuck that is now used almost universally in the UK. Nevertheless, I particularly enjoyed the section on central venous access; the author reviews a vast volume of literature on reported series of almost 13 000 catheterizations with a mean complication rate of 11 per cent. It is regrettable that Grant has not used SI units in this book as this makes many of the measurements and serum levels unintelligible without calculations. Similarly, the nutrients available in the USA differ considerably from those available in Europe.

Despite these reservations, this is an excellent reference textbook and should be available to all clinicians called on to feed patients intravenously. Gastrointestinal surgeons may find it particularly useful and may want to have their own copy.

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The Management of Wounds and Burns

J. Wardrope and J. A. R. Smith. 215 × 140 mm. Pp. 238. Illustrated. 1992. Oxford: Oxford University Press. £13·95.

This is one of a series of handbooks in emergency medicine reflecting a long overdue and welcome concern about the hitherto silent epidemic of trauma. A staggering figure of 11 million patients attend accident and emergency departments in the UK each year, of whom over 3 million have a wound of some form or other. The authors have aimed this volume primarily at junior doctors and nurses working in accident and emergency. Nevertheless, any doctor, regardless of seniority or specialty, likely to be called on to treat a wound would do well to read this valuable book from cover to cover and to retain the wealth of practical information that it contains. Wound management unjustly receives scant attention in training nowadays. The format is clear, concise and well illustrated, and the book fits neatly inside a coat pocket. Wound assessment and treatment, and the management of special types of wound, including those of the hands and face, are covered in detail. Burns receive similarly detailed coverage. I commend this book to any doctor or nurse working in an accident and emergency department as the best insurance against patients suffering needless harm after sustaining a wound. It will have pride of place in our department library and I expect it will be frequently consulted. Even better, each member of staff should buy their own copy.

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Advances in Surgery

J. L. Cameron, C. M. Balch, B. Langer, J. A. Mannick, G. F. Sheldon, G. T. Shires, R. K. Tompkins and C. E. Welch. 235 × 158 mm. Pp. 371. Illustrated. 1992. St Louis, Missouri: Mosby–Year Book. £44.

The latest *Advances in Surgery* represents the 25th edition of a book whose original aim was to be ‘a publication devoted to new subjects explored in depth’. It is aimed at practising surgeons, surgeons in training and medical students. Editors of any ‘recent advances’ books always have a problem since by the time of publication the advances no longer seem recent. The chapter on laparoscopic cholecystectomy suffers badly in this regard. None the less, several of the chapters succeed in giving an excellent and up-to-date overview of their subject. Those on adjuvant therapy for colonic cancer and current diagnosis and management of upper gastrointestinal bleeding are particularly good. I was disappointed at the lack of editorial control on chapter content. Some chapters (‘Benign bile duct strictures’, ‘Whipple’s operation’) include considerable operative detail whereas others have little or no such content. Chapters also vary in length from 11 to 49 pages; reference numbers range from ten to 199. Approximately 10 per cent of the references come from British or European journals. Neither I nor any of my colleagues on this side of the Atlantic knew the word ‘bariatric’ in relation to surgery of the morbidly obese. Overall the book is well written and well illustrated. I suspect that relatively few individual surgeons in the UK would wish to buy it but several chapters are worth reading if the book appears in the hospital library.

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Operative Cancer Surgery. Vol. 1: Gastro-intestinal Tract

I. Burn and J. McK. Wellwood (eds). 302 × 212 mm. Pp. 227. Illustrated. 1992. London: Farrand Press.

The first question when reviewing a book like this is: ‘Is there such a thing as cancer surgery?’ The answer, I believe, is ‘yes’. The patient with cancer presents problems that are different from those seen with benign disease. Unfortunately, in the main, I found this book to be disappointing because it does not address these issues. The volume would be unhelpful to the specialist working in the field and, frankly, misleading to the trainee. It suffers as a multiauthor work in unevenness and imbalance in how the various topics are covered; for example, the chapter on gastric cancer is shorter than that on the small intestine.

The overall impression is that this is an old-fashioned book. This can be seen in the chapter on the colon, which suggests a 5-day bowel preparation regimen and the use of a suturing needle big enough to be held in the fingers. Surely this is not what we would encourage our trainees to do in the age of human immunodeficiency virus. Much of this book reflects the surgery of a decade ago, as witnessed by the long explanation on how to perform a transverse colostomy (an operation in my experience that is rarely used these days) but only three lines dedicated to the possibilities of resecting metastatic disease in the liver. There are positive aspects to the volume. By and large, the illustrations are clear and informative and add to the text. I enjoyed the chapters on the pancreas, liver, gastric cancer and on gastric reconstruction. Apart from this, the book does not contribute any more than can be found in the existing standard operative surgery guides and in most part is of less value; it will do little to persuade surgeons that there is a subspecialty of surgical oncology.

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Surgery of the Arteries to the Head

R. Berguer and E. Keiffer. 280 × 220 mm. Pp. 236. Illustrated. 1992. Heidelberg: Springer-Verlag. DM 368.

The past 5 years have seen a number of textbooks on vascular surgery, usually multiauthor. This one, however, is written by only two, a Frenchman and an American, well known for their technical excellence and interest in head and neck arterial surgery. Between them they have an unrivalled experience of these procedures.

This is essentially a book on technique, an outstanding feature of which is the copious and beautifully coloured line drawings and illustrations on anatomy, exposure, operative procedures and so forth. Indeed, in terms of content these represent a major part of the book, the written text being a secondary consideration. None the less, the latter is filled with technical tips, variations of exposure and a goldmine of ingenuity and improvisations.

What are the limitations of the book? It is focused on a field that, for most British vascular surgeons, is almost exclusively carotid endarterectomy – an operation that poses few specific technical problems. Thus a large proportion of the book devoted to vertebral artery and supra-aortic reconstruction is of limited interest. Furthermore, the authors have discussed to only a minor degree the clinical presentation, workup, investigations, indications and results. Increased emphasis on these aspects would have been helpful. There are few references.

In summary, this is an outstandingly illustrated, specialized and technical book for the surgeon with a major interest in vascular surgery.

S. G. Darke

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UK

Motility Disorders of the Gastrointestinal Tract. Principles and Practice

S. Anuras (ed.). 242 × 158 mm. Pp. 479. Illustrated. 1992. New York: Raven Press. US$122·50.

It was a great pleasure to review this book, which approaches motility disorders of the gastrointestinal tract in an objective and scientific manner. The text is very readable, well illustrated and, as may be expected with contributions from 22 specialists on gastrointestinal motility, authoritative. Furthermore, the quality of the illustrations is high and the bibliography impressive.

The first two chapters review the structure of the alimentary tract and the mechanisms by which gastrointestinal motility is regulated. This section is followed by four chapters describing the methodologies used to investigate aspects of gastrointestinal motility together with a critical evaluation of their usefulness and limitations. In general the various techniques available for assessing gastrointestinal motility are comprehensively and adequately described, with the possible exception of the increasing interest in the use of ultrasonography. For example, there is no reference to the use of endoanal ultrasonography in the assessment of the anal sphincter complex as an alternative to electromyography.

The remainder of the book is devoted to a critical appraisal of generalized and localized gastrointestinal dysmotility and abnormalities in motility associated with specific clinical syndromes. I was particularly impressed with these sections, in which the authors approach each aspect of gastrointestinal dysmotility in a refreshingly objective and logical manner. My only criticism would be the omission of motility dysfunction as a contributory factor in the pathogenesis of gastro-oesophageal reflux disease. Despite such minor omissions, this is an invaluable book for gastrointestinal surgeons and trainees, particularly those with a research interest in motility, as a source of information and reference.

S. A. Jenkins

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Specialty Medical Audit

C. D. Shaw. 209 × 148 mm. Pp. 206. Illustrated. 1992. London: King's Fund. £7·50.

Dr Charles Shaw, currently Director of the Bristol Clinical Audit Unit and Senior Lecturer in Epidemiology and Community Medicine at the University of Bristol, has produced a compilation of the existing organizations available for medical audit and of the resources approachable for funding to support the process. The book gives specific references that are, as yet, uncommon in audit literature and lists sources from which doctors can obtain ideas for audit projects.

Specialty Medical Audit concentrates on hospital-orientated activities and does not include general practice- or community-based disciplines. In addition to specific projects related to accident and emergency medicine, anaesthetics and intensive care, clinical oncology, general and geriatric medicine, obstetrics and gynaecology, paediatrics, psychiatry, radiology and surgery, there are general chapters on national guidance, organization, methods and resources. The chapters on specialty audits each follow the same format, starting again with guidance about existing national strategies, organizational aspects and methods and resources currently existing for each specialty, followed by specific examples of audit projects in that discipline. Each chapter is individually referenced and, as the author implies in the introduction, supports the fact that it is good practice to educate oneself about what is happening in other specialties since their audit projects and ideas may spawn new thoughts. For this reason alone this easily readable book could be thoroughly recommended, especially for hospital and university libraries where junior doctors and those new to audit processes can readily have access.

G. Davies

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UK

Clinical Paediatric Urology. Vols 1 and 2. 3rd ed.

P. P. Kelalis, L. R. King and A. B. Belman (eds). 260 × 185 mm. Pp. 1467. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US$225.

Paediatric urology continues to evolve as a distinct specialty and the third edition of this book maintains its claim to be the definitive text for the specialty. The contributing authorship, however, is exclusively North American as manifest by the bias afforded topics such as neonatal circumcision and vesicoureteric reflux; scant attention and emphasis are given to the British and European contributions to this field. The preface admits to failure at encyclopaedic review but there are a number of omissions, with varicocele being a surprising one (and I suspect an oversight), and the absence of any prescriptive guidelines in the management of prenatally detected hydronephrosis, a disappointing omission.

Editorial scrutiny has failed to identify two separate chapters each dealing with multicystic kidney and a similar duplication exists in the surgical management of intersex. Moreover, the presentation of bibliographies following each chapter is inconsistent. The titular indexing of some chapters is misleading: 'Anomalies of the renal pelvis and ureters' fails to include ureteropelvic junction stenosis, this subject being located under the heading 'Obstructive uropathy'. I would have preferred a substantial contemporary text in paediatric urology to have also included comment on the adolescent and adult consequences of childhood anomalies, particularly in relation to genital disorders. This book does not do so to any great extent.

These considerations apart the book provides sufficient authoritative contribution and review to distinguish itself from others in this field and maintains its status as a definitive reference and learning volume on the subject of paediatric urology. It will find its way to the departmental library of surgeons working in this field and will be easily read by paediatric surgeons and paediatric surgical trainees alike.

G. G. Youngson

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Atlas of Operative Surgery. Surgical Anatomy, Indications, Techniques, Complications: Gallbladder, Bile Ducts, Pancreas

K. Kremer, W. Lierse, W. Platzer, H. W. Schreiber and S. Weller (eds). 300 × 230 mm. Pp. 260. Illustrated. 1992. Stuttgart: Georg Thieme. DM 360.

It was a joy to read this book which, like a good thriller, was difficult to put down. Although the majority of the contributors are German, I was struck by the quality of the translation, which was clear and easily understood, lacking any didactic prose.

I was particularly struck by the quality of the artwork and the diagrams, which were all in colour and gave a feel for the operations described. The only section that failed to live up to the high standard set by the atlas was that on laparoscopic cholecystectomy, where the diagrams failed to capture the quality of image that we have now become used to on our videoscreens. Peroperative cholangiography, during either open or laparoscopic cholecystectomy, is hardly mentioned, but pressure manometry of the bile duct using techniques little improved on since those described by Caroli in 1946 for the diagnosis of 'papillary spasm' is given high profile.

The authors have been careful not to describe too many operative techniques, but concentrate instead on surgical conditions that are more commonly encountered by the average surgeon. This book provides information on more than just operative surgery, covering endoscopic and percutaneous techniques and introducing each section with detailed surgical anatomy. I think it is invaluable for those embarking on specialist surgical training and will be much enjoyed by practising surgeons who specialize in hepatobiliary and pancreatic surgery.

B. F. Ribeiro

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Notices and announcements

4–9 July 1993
Endosurgery – the State of the Art
Hamilton Island, North Queensland, Australia
Information: Kathy Noble, Centre for the Study of Endosurgery, Department of Surgery, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

5–8 July 1993
First International and Eighth European Conference on Clinical Hemorheology
Vienna, Austria
Information: Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Währinger Gürtel 18–20, 1097 Vienna, Austria

6 July 1993
Current Issues in Epidemiology: the Prevention and Control of Chronic Disease
Cambridge, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

6–17 July 1993
Current Practice in Neonatal and Paediatric Surgery
Manchester, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

8–9 July 1993
Surgical Research Society Meeting
Dundee, UK
Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 July 1993
XVIIIth International Update on Liver Disease
London, UK
Information: Professor N. McIntyre, University Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

8–10 July 1993
5th South-east European Symposium of Paediatric Surgery
Graz, Austria
Information: Professor M. E. Höllwarth, Department of Paediatric Surgery, University of Graz, Heinrichstraße 31, A-8010 Graz, Austria

19–24 July 1993
Second United European Gastroenterology Week
Barcelona, Spain
Information: Professor J. R. Malagelada, Calle Calvet 55–57, 08 021 Barcelona, Spain

6–8 August 1993
First Asian Pacific Congress of Endoscopic Surgery
Singapore
Information: Maggie Phang, Congress Secretariat, Conference and Exhibition Management Services, 09-43 World Trade Centre, Singapore 0409

11–14 August 1993
27th Malaysia–Singapore Congress of Medicine
Kuala Lumpur, Malaysia
Information: Organizing Committee, Level 5, MMA House, 124 Jalan Pahang, 53 000 Kuala Lumpur, Malaysia

22–28 August 1993
35th World Congress of Surgery of the International Society of Surgery
Hong Kong
Information: Scientific Secretariat, c/o ISS/SIC, Hauptstraße 63, PO Box 411, CH-4153, Reinach BL 1, Switzerland

27–29 August and
30 August–2 September 1993
Second International Conference of Gastroenterology
Hong Kong and Chengdu, China
Information: Conference Secretariat, Room 1611-13, World Finance Centre, North Tower, Harbour City, Kowloon, Hong Kong

1–3 September 1993
4th International Congress – International Organization for Statistical Studies on Diseases of the Oesophagus
Paris, France
Information: Michele Liegeon, 2 Boulevard de Montparnasse, 75 015 Paris, France

2–4 September 1993
Second International Workshop: Inflammatory Bowel Disease
Treviso, Italy
Information: Dr G. Di Falco, Divisione Chirurgica III, Ospedale Regionale Generale 'Ca' Foncello', 31 100 Treviso, Italy

7–10 September 1993
6th International Congress on Interventional Ultrasound
Copenhagen, Denmark
Information: Dr C. Nolsøe, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

10–11 September 1993
Frontiers in Transplantation and Medical Treatment of Liver Disease
Hamburg, Germany
Information: Marion Schemnitzer, Master-Media GmbH, Bodelschwinghstraße 17, D-2000 Hamburg 63, Germany

14–17 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

15–17 September 1993
Nottingham European Organization for Research and Treatment of Cancer Joint Breast Cancer Meeting
Nottingham, UK
Information: Mrs Wendy Bartram, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

29 September to 1 October and
2 October 1993
Principles of Colon and Rectal Surgery, and Biofeedback for Pelvic Floor Disorders/Endorectal Ultrasonography
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue South-east, Minneapolis, Minnesota 55414, USA

17–23 October 1993
Surgery of the Liver, Biliary System and Pancreas
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

18–19 November 1993
Vascular Surgical Society of Great Britain and Ireland Annual Meeting
Manchester, UK
Information: Mr P. L. Harris, VSS Secretary, Vascular Unit, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

30 November to 2 December 1993
Eighth International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr S. C. S. Chung, Combined Endoscopy Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title page should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies of original articles and other editorial matter to: The Senior Editor, *The British Journal of Surgery*, Butterworth–Heinemann Ltd, 59/60 Grosvenor Street, London W1X 9DA, UK. Telephone: 071-493 5841. Facsimile: 071-499 3384.
Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 500 words, with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

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The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

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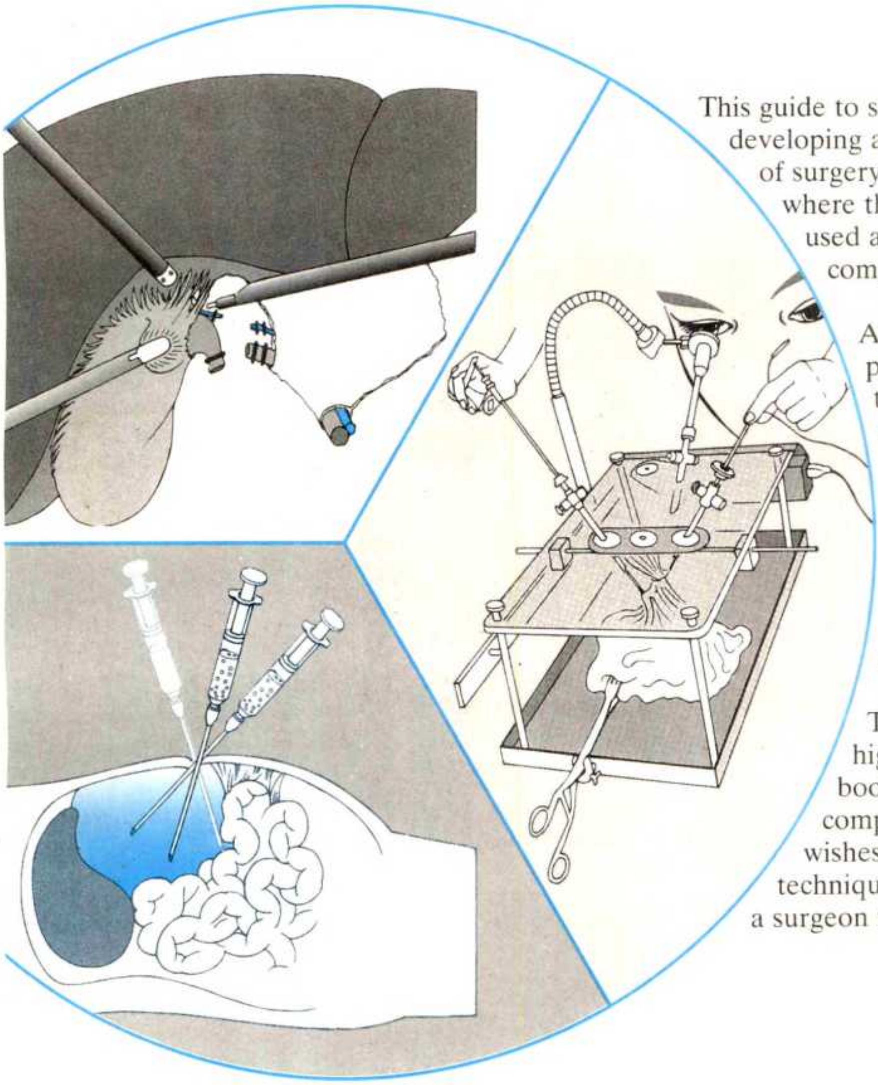
A. Cuschieri, Dundee; **G. Buess,** University of Tübingen; **J. Périssat,** Bordeaux (Eds.)

Operative Manual of Endoscopic Surgery

1992. X, 353 pp. 378 figs. in 561 sep. illus., 171 in color. 20 tabs. Hardcover DM 307,– ISBN 3-540-53486-5



This guide to surgery is dedicated to a rapidly developing and continuously expanding area of surgery. All indications and conditions where this state-of-the-art method can be used are treated systematically in this comprehensive work.

All of the authors and editors are pioneers of worldwide repute in their respective techniques. Special emphasis has been placed on highly informative diagrams which form an instructive complement to the numerous accompanying "real-time" figures taken directly during operative procedures through the endoscope.

The clear text and the impressive high-quality illustrations make the book an essential and unique companion for every surgeon who wishes to become familiar with the new techniques which today's patients expect a surgeon to know.

The contents feature
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- Technical equipment including future developments
- Thoracoscopic procedures
- Gastrointestinal endoscopic procedures
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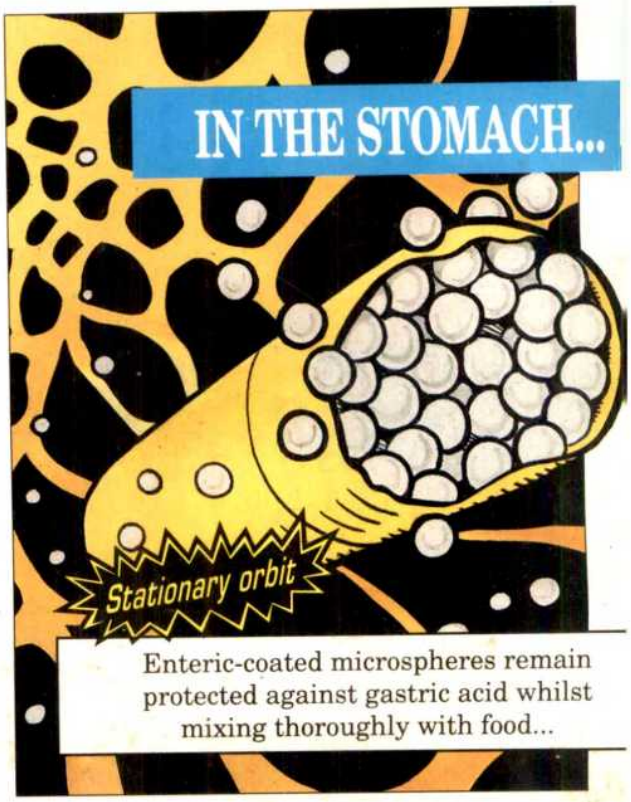
A REAL FORCE IN PANCREATIC EXOCRINE INSUFFICIENCY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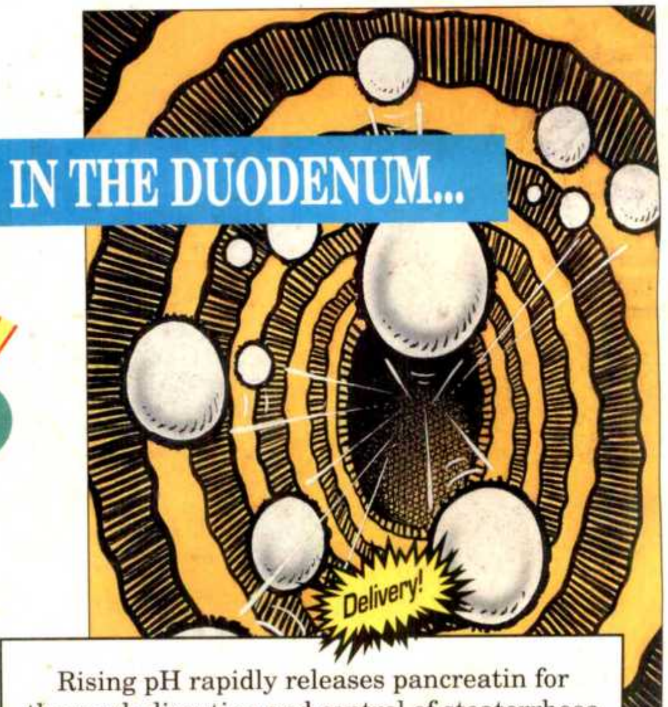
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References

1. Stead R J et al. *Thorax* 1987; **42**: 533-37
2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

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Volume 80 Number 6 June 1993

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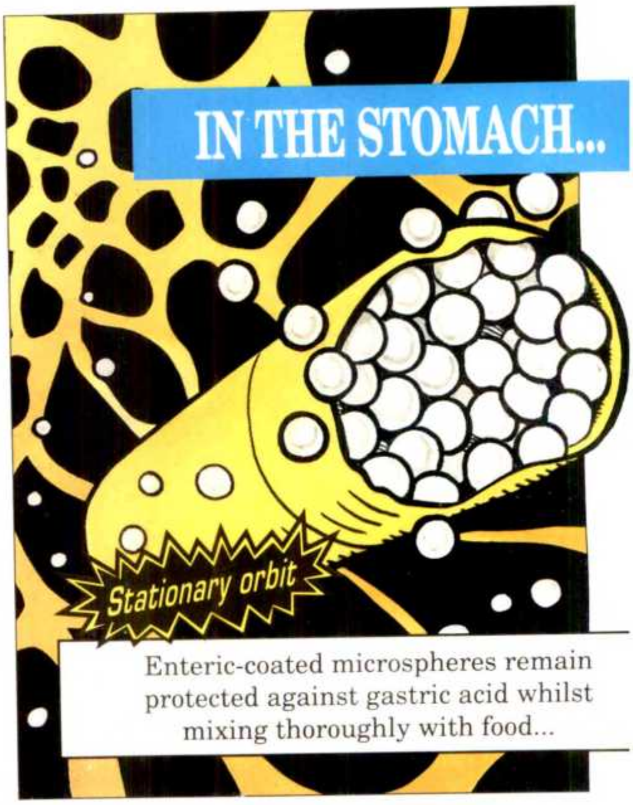
A REAL FORCE IN PANCREATIC EXOCRINE INSUFFICIENCY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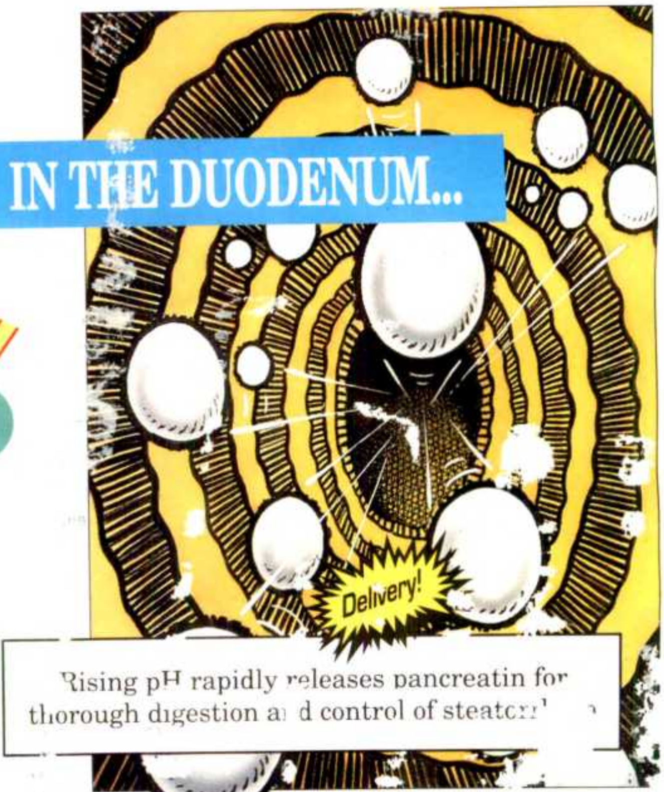
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Date of last review January [illegible]

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1. Stead R J et al. *Thorax* [illegible] 533-37
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Profile of Mood States (POMS) was use to assess such feelings as tension, depressio fatigue and vigour, while Functional Livin Index: Cancer (FLIC) was used to measu physical ability, sociability, emotional sta and family interaction.

The results of this study suggest that on the patient group treated with 'Zolade maintained a higher level of quality of li compared to their pre-treatment values.

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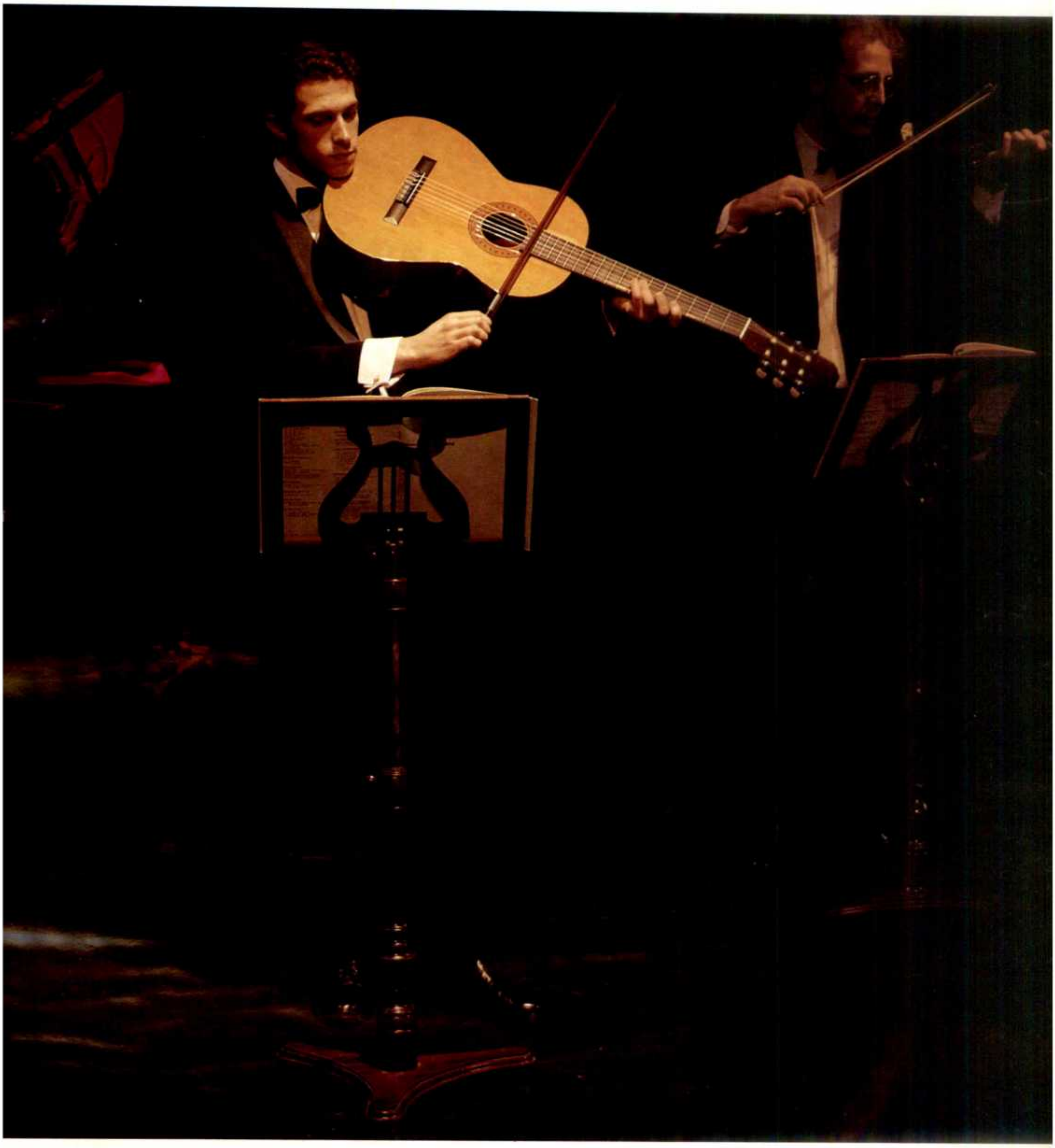

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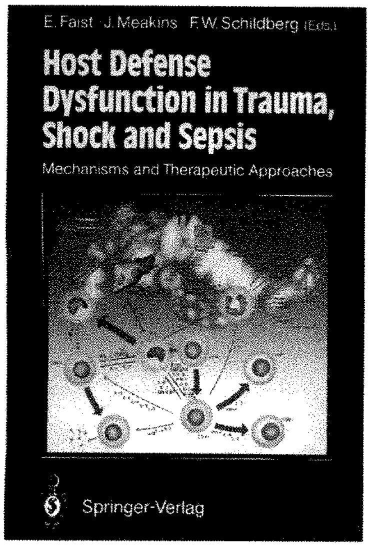
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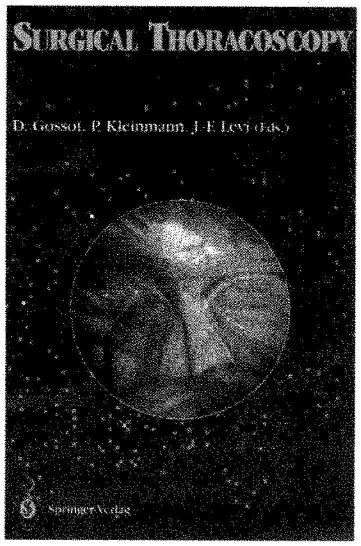

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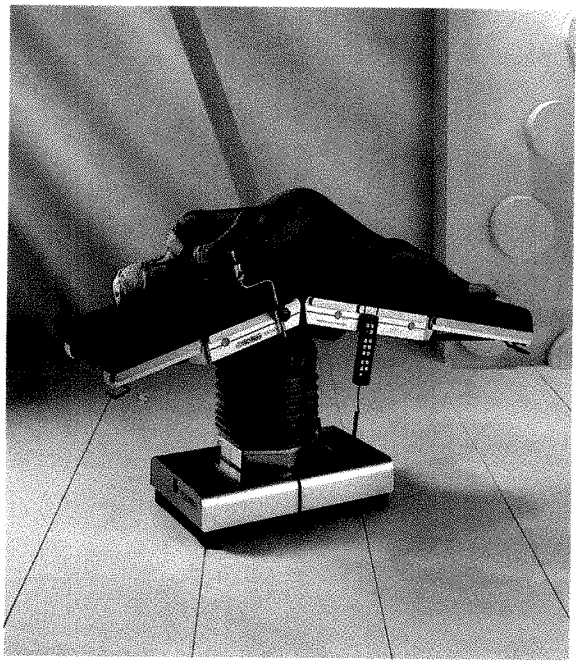

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Editors' announcement

Dual publication/submission

An instance of dual publication and one of dual submission have recently been uncovered by the Editorial Team:

1. Delaitre B, Maignien B, Icard Ph. Laparoscopic splenectomy. *Br J Surg* 1992; **79**: 1334.

   Delaitre B, Maignien B. Laparoscopic splenectomy – technical aspects. *Surg Endosc* 1992; **6**: 305–8.

2. Byrne DJ, Napier A, Cuschieri A. The value of whole body disinfection in the prevention of postoperative wound infection in clean and potentially contaminated surgery. A prospective, randomised, double-blind, placebo-controlled clinical trial. *Surgical Research Communications* 1992; **12**: 43–52.

   Byrne DJ, Napier A, Cuschieri A. Prospective randomized placebo-controlled double-blind trial of whole-body disinfection with chlorhexidine in the prevention of postoperative wound infection in elective surgery. (Submitted to *The British Journal of Surgery*, passed through referees and the editorial process but arrested at proof stage; dual publication was averted at the last moment.)

Full apologies have been received by the Journal from Professor Delaitre and Mr Byrne. The Editors draw attention to two specific problems other than the tedium and repetition associated with dual publication.

Authors may well be infringing copyright regulations by indulging in dual publication and some journals may take a legal stand in this situation. The articles do not need to be identical for infringement of copyright to occur.

The second example was associated with a mechanism of publication that seems to be occurring more frequently. Authors at meetings are often asked to submit a manuscript at the time of presentation of a paper. The paper published in *Surgical Research Communications* was handed to the recorder at the Annual Meeting of the Surgical Infection Society of Europe held in Athens in 1991. The authors corrected and signed proofs for publication in *Surgical Research Communications*.

Investigators and senior authors need to think carefully when asked to provide a manuscript to support an oral presentation. If such manuscripts are subsequently to be considered by *The British Journal of Surgery* they should not be handed in at meetings as this almost certainly signals potential publication elsewhere.

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Br. J. Surg. 1993, Vol. 80, June, 682–683

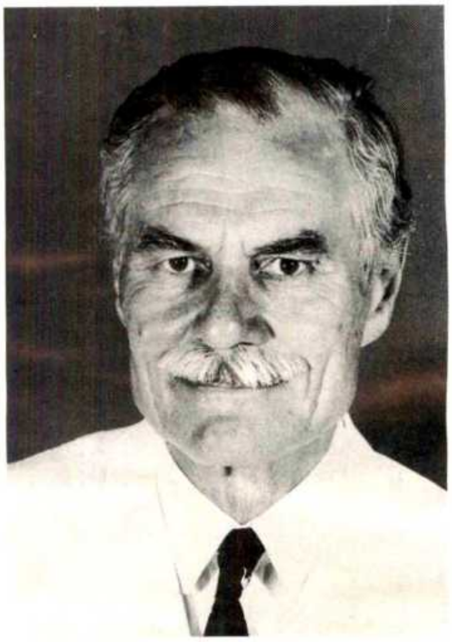
Continuing our series of profiles of Board Members from around the world.

PROFESSOR BOB VAN HEE
(Belgium)

Robert Van Hee (born 1943) is Professor of Surgery at the University of Antwerp and a consultant surgeon at the University Hospital in that city. He graduated from Ghent and obtained a higher degree (MD) on pancreatic transplantation at the University of Nijmegen in the Netherlands. He has been Secretary-General and now Vice-President of the Royal Belgian Society for Surgery. He is interested in gastric, pancreatic and transplantation surgery as well as the history of medicine.

PROFESSOR MICHAEL TREDE
(Germany)

Michael Trede was born in Hamburg in 1928 and came to England shortly before the Second World War. Graduating from Cambridge University and the Middlesex Hospital, London, he returned to Germany as an officer in the Royal Army Medical Corps. He trained in Berlin, Heidelberg and Los Angeles before being appointed Professor and Chairman of Surgery at Mannheim (University of Heidelberg) in 1972. He is recognized chiefly for his work in pancreatic surgery. Professor Trede is President-Elect of the International Society of Surgery.



PROFESSOR JEAN-CLAUDE GIVEL
(Switzerland)

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Robin Williamson

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Endothelial xanthine oxidase: a radical transducer of inflammatory signals for reticuloendothelial activation

The ubiquity of free radicals and other reactive metabolites of oxygen in biological systems and their role as a final common mediator of tissue injury in a broad variety of disparate disease processes have come to be widely appreciated, as summarized recently in this Journal[1] and described more extensively elsewhere[2,3]. Moreover, it is now understood that the high reactivity of these oxidant species has often been exploited by natural selection in the evolution of physiological and pathophysiological mechanisms advantageous to survival. Such mechanisms include the metabolism of arachidonic acid for the generation of prostaglandins and leukotrienes, the killing of micro-organisms by phagocytes, the detoxification of xenobiotics, ovulation, fertilization and even the oxidative generation of energy as adenosine 5′-triphosphate by the mitochondrial respiratory chain[1–3]. It now appears likely that the enzyme xanthine oxidase, because of its unique ability to trigger the rapid generation of superoxide free radicals, plays an important, perhaps primary, physiological role in activation of the reticuloendothelial system. If this hypothesis proves to be correct, then xanthine oxidase may serve as a primary molecular switch for control of this inflammatory response, a role analogous to that of cyclic adenosine 3′,5′-monophosphate in the response to hormonal stimulation.

Xanthine oxidase is translated in the form of a 150-kDa protein, xanthine dehydrogenase[4], which catalyses the terminal oxidation of purines (hypoxanthine and xanthine) to uric acid, coupled with the reduction of nicotinamide adenine dinucleotide (NAD^+) to NADH. Because no free electrons are generated, no reactive oxygen metabolites are produced. The dehydrogenase enzyme is remarkable, however, in that it can be converted from this constitutive form to xanthine oxidase, usually by the irreversible limited proteolytic cleavage of a 26-kDa peptide[5]. Although xanthine oxidase also catalyses the oxidation of purines to uric acid, this oxidation must be coupled with the reduction of molecular oxygen rather than NAD^+. When the extra electron is passed to oxygen, the highly reactive superoxide free radical anion is generated.

The initial discovery of a clinically relevant consequence of xanthine oxidase activation was related to its activation by ischaemia, facilitating a burst of superoxide radical generation when oxygen was reintroduced at reperfusion[2]. Subsequent studies, primarily by Granger and colleagues, have indicated that, although it is fairly reactive, the superoxide radical itself is often not the final agent of reperfusion injury[2,3]. Instead, it triggers the generation of a cascade of toxic oxidants, a characteristic free radical-mediated chain reaction that signals the integrin-mediated adhesion, trapping and activation of circulating neutrophils, with consequent microvascular injury which is manifest ultimately as parenchymal organ injury and dysfunction[2]. We have recently found that this superoxide signal may also be transduced into changes in gene expression, manifest as the transcription of the messenger RNA for heat-shock proteins. Thus, the initial generation of superoxide serves not so much to produce injury directly, but rather to trigger an intricate cascade of biochemical and pathophysiological events; these ultimately act via the trapping and activation of neutrophils by the microvascular endothelium. Indeed, neutrophil accumulation in postischaemic tissue is blocked by xanthine oxidase inhibition with allopurinol[2].

Although neutrophils and macrophages generate superoxide from oxygen to facilitate the killing of organisms on the outer surface of their plasma membrane, and thus within phagosomes, using a highly specialized membrane-associated NADH oxidase[6], they contain little or no detectable xanthine oxidase and this 'respiratory burst' is not attenuated by xanthine oxidase inhibition[2]. Nor are the neutrophils that enter the postischaemic organ at reperfusion present within that organ during ischaemia. Therefore, neutrophils are an unlikely source of the xanthine oxidase-generated superoxide that triggers reperfusion injury. However, xanthine oxidase is

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abundant within the microvascular endothelium of all organs studied (including the human heart and brain in which parenchymal levels of xanthine oxidase have been difficult to detect[7]). Indeed, the entire xanthine oxidase-based superoxide-mediated trigger mechanism is complete and operational within endothelial cell monolayers. Here, as *in vivo*, the endothelial trigger mechanism can be activated by anoxia via xanthine dehydrogenase to oxidase conversion[8]. More recently, we have found that the enzyme is expressed constitutively, as xanthine dehydrogenase, both in the cytoplasm and on the outer surface of the endothelial cell plasma membrane[9]. This localization explains the observed, but heretofore unexplained, rapid pharmacological accessibility of circulating (extracellular) high molecular weight antioxidants such as superoxide dismutase, both in animal studies and in at least one clinical trial[3].

These observations lead to the question: What selective advantage, conferred by such an elaborate cascade mechanism, has driven its evolution and ubiquitous conservation within the genome? Not only is reperfusion unlikely in nature, the mechanism is injurious not salutary. I have proposed (American Association of Endocrine Surgeons' Meeting, San José, California, USA, April 1991) that this mechanism has been favoured by natural selection to trigger the trapping and killing of circulating pathogenic micro-organisms within the microvasculature; it would thereby constitute a major effector of reticuloendothelial function. Its triggering by limited proteolysis is a conventional pathophysiological strategy for more rapid activation than could be achieved by change in gene expression. In this way it would be analogous to activation of the clotting cascade, the complement system, the renin–angiotensin system and protein kinase-activated intracellular control systems. The fact that interferon γ increases the expression of xanthine dehydrogenase in endothelial cells suggests that there may also be a slower component of this activating response. The predominant localization of (postischaemic) neutrophil adhesion within the venule, where the blood flow is slowest, would facilitate the initial arrest of circulating micro-organisms. The fact that the rapid activation of xanthine oxidase from xanthine dehydrogenase may be effected in endothelial cells by cytokines (tumour necrosis factor α, interleukin types 1 and 3), complement (C'5a), proteases (neutrophil elastase, chymotrypsin), mitogens, bacteria, endotoxin and oxidants themselves *in vitro*[10] supports the concept that activation of xanthine oxidase on the cell surface represents a common mechanism of inflammatory signal transduction. It would transduce circulating inflammatory signals (cytokines etc.) via superoxide generation to effect the integrin-mediated adhesion and activation of neutrophils within the microvasculature, thereby activating reticuloendothelial function in peripheral organs. If this is true, reperfusion injury represents a pathological extreme caused by the aberrant activation of endothelial xanthine oxidase by ischaemia.

This hypothesis represents a possible primary control mechanism for the rapid activation of reticuloendothelial function. It might also provide the pathophysiological basis not only for reperfusion injury, but also for a number of other important medical conditions, including multiple organ failure which is characterized by sequential organ dysfunction associated with microvascular inflammation and injury, and with massive increases in levels of circulating inflammatory mediators. Moreover, the ease with which such a mechanism may be controlled pharmacologically, without toxicity, provides a substantial potential for therapeutic benefit[3].

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Publisher's announcement

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Endoscopic sympathectomy

Sympathetic denervation of the upper limb has been carried out for many years and, because of the relative inaccessibility of the upper dorsal sympathetic chain, by many different approaches. At first, sympathectomy was usually performed for vasospastic conditions of the fingers, but the long-term results were disappointing and so limited the popularity of the procedure. Conversely, sympathectomy usually provides a permanent cure for idiopathic hyperhidrosis in the form of excessive sweating from the palms or axillae. Patients with sweating severe enough to cause significant occupational, educational, or social and psychological difficulties who have been cured by sympathectomy are among the most grateful that surgeons will encounter in the course of their work. Most describe their life as being 'completely changed' by the operation.

Despite this, many surgeons have been reluctant to undertake what can be a difficult technical procedure, carrying a definite morbidity, for a condition that does not threaten life or limb. It is against this background that a search has been continued for simpler, less invasive and safer methods of performing sympathectomy. Reid *et al.*[1] in 1970 described chemical sympathectomy using phenol injection via the second intercostal space, but many have not been able to reproduce their excellent results. Kux[2] in 1978 described an endoscopic approach, first inducing pneumothorax under local anaesthesia and then excising the upper dorsal sympathetic chain, from the second to sixth dorsal ganglion inclusive, through a thoracoscope using scissors and hooks. He operated on one side only at a sitting. Since then, techniques have been refined and it is now usual to carry out the procedure under general anaesthesia, using a standard laparoscope and simple diathermy, although some employ a laser. Both sides can be dealt with at the same session without any problem[3–5].

Modern results are excellent, with a 92 per cent initial success rate. Operating time is short and the technique is easily learned by anybody with endoscopic experience. The view of the sympathetic chain obtained by this approach is better than that provided by any of the open procedures. An important feature from the patient's point of view is the lack of significant postoperative pain. Most patients leave hospital the day after operation (or even on the same day) and can return to their usual activities a day or two later. Many are young women; the scars of the endoscopic procedure are cosmetically far superior to those of other approaches. Complications are few; the very occasional pneumothorax requires a chest drain and there is a low incidence of transient intercostal neuralgia[5]. Permanent Horner's syndrome has not been reported, unlike after operative methods, and the recorded incidence of transient Horner's syndrome appears to be low[5].

The only absolute contraindication to endoscopic sympathectomy is the presence of dense apical pleural adhesions, which cannot always be excluded by preoperative chest radiography. However, fine adhesions can be divided easily during the procedure. Constitutional causes of excessive sweating must, of course, be ruled out before surgery is considered. Recurrence of sweating has been reported in a small percentage of cases[4] and can be treated by reoperation without much difficulty.

The one significant side-effect of sympathectomy is compensatory sweating from other parts of the body, usually the waist, back of the trunk or thighs. This is reported as occurring in 48–64 per cent of patients[2,5] but is almost invariably considered by those affected as infinitely preferable to the previous palmar or axillary hyperhidrosis. It is usually, but not always, related to the extent of sympathectomy. In recent times the procedure has been limited in the author's department to the second and third dorsal ganglia, and a reduction has been observed in the incidence of compensatory sweating. O'Riordain *et al.*[6] have also recently shown that excision of only the second dorsal ganglion may be sufficient to abolish palmar sweating and reduce that from the axilla. Gustatory sweating in the head after hot or spicy food has been highlighted in some reports but is curiously absent from others[2,5,7].

Considerable confusion still exists in the literature about the precise anatomical connections of the sympathetic nervous system in this region; it appears that there is much variation both among patients and between one side and the other in the same patient[8,9]. Such variation has probably contributed to some of the problems following open operations, as the view of the anatomy at such procedures is never as good as that through the endoscope.

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Endoscopic sympathectomy has now stood the test of time. It is easier to perform and so safer than open procedures. It is far more comfortable for the patient, cosmetically superior and costs less.

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Review

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Prophylaxis of postoperative thromboembolism with low molecular weight heparins

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To evaluate the thromboprophylactic use of low molecular weight heparins (LMWHs), publications from 27 orthopaedic trials and 35 studies of patients undergoing general or gynaecological surgery were scrutinized and subjected to a partial meta-analysis. In orthopaedic surgery, LMWHs were superior to placebo or dextran and at least as efficient as unfractionated heparin in the prevention of deep vein thrombosis (DVT). Compared with unfractionated heparin, one of the LMWH preparations significantly reduced the total incidence of DVT. The rate of non-fatal pulmonary embolism was 0·49 per cent in patients receiving LMWH and 1·22 per cent in controls. Seven orthopaedic patients (0·15 per cent) died from pulmonary embolism, none of whom received LMWH. In general surgery, the LMWHs were at least as efficient as unfractionated heparin, with a trend towards a lower risk of pulmonary embolism with the former. Compared with unfractionated heparin, LMWHs did not reduce the postoperative mortality rate, nor did they cause haemorrhage. LMWHs provide safe and efficient prophylaxis by administration once daily.

The use of conventional low-dose unfractionated heparin is a well established method in the prevention of postoperative thromboembolic complications. The administration of low doses of heparin has reduced the incidence of postoperative deep vein thrombosis (DVT) and even fatal pulmonary embolism[1,2]. However, some types of surgery, especially orthopaedic, still carry an unacceptably high risk of DVT, reported by some to be about 30 per cent despite the use of unfractionated heparin in combination with dihydroergotamine (DHE)[3]. Furthermore, the administration of unfractionated heparin is associated with certain side-effects such as an increased bleeding tendency (albeit seldom of clinical significance), allergic manifestations, alteration of platelet function and changes in levels of lipoprotein lipase and liver lipase[4].

Unfractionated heparin is a heterogeneous mixture of molecules of different molecular weights, ranging from 3 to 40 kDa, and with varying amounts of specific biological activity depending on molecular structure and size. Low molecular weight heparins (LMWHs) are derived from unfractionated heparin by either enzymatic cracking or filtration; LMWHs are believed to possess lesser effects on overall clotting as reflected in activated partial thromboplastin and thrombin clotting time assays[5].

Experimental studies have led to the theory that antifactor Xa activity correlates with antithrombotic efficacy, whereas antifactor IIa activity relates to the influence on bleeding. LMWHs have less ability to inactivate thrombin relative to their capacity to inhibit factor Xa, as the inactivation of thrombin by heparins is dependent on the size of the heparin molecule. The specific antifactor Xa:antifactor IIa activity ratio for LMWHs is thus higher than for unfractionated heparin. Therefore, in equipotent antithrombotic doses, LMWHs should cause less bleeding than unfractionated heparin; this has been verified only in animal models[6,7]. Compared with unfractionated heparin, LMWHs exhibit a different pharmacokinetic profile with a longer half-life and higher bioavailability. Also, the suppression of platelet aggregation by LMWHs[8] and their affinity for several plasma proteins are less pronounced[9].

During the past 7 years, several clinical studies using LMWHs for thromboprophylaxis in surgical patients have been published. Controlled trials have been carried out with the following LMWH products: Fluxum (Alfa LMWH; Alfa Farmaceutici, Bologna, Italy), Clexane (Enoxaparin; Rhône-Poulenc Rorer, Gennevilliers, France), Fragmin (Dalteparin; Kabi Pharmacia, Stockholm, Sweden), Fraxiparin (CY216; Sanofi, Paris, France), Logiparin (Tinzaparin; Novo Nordisk, Bagsværd, Denmark) and Sandoparin (Sandoz LMWH; Sandoz, Nuremberg, Germany). Although there are differences between the LMWHs used[10], the type of operations and the methods of screening for DVT, the present aim is to obtain an overall impression of the clinical value of LMWHs in thromboprophylaxis by analysing the available data.

Methods

To diminish the risk of publication bias[11], this analysis tried to include all published reports, including abstracts from conferences, of randomized controlled trials using LMWHs for thromboprophylaxis in orthopaedic, general or gynaecological surgery. Trials in which the recently developed heparinoids or dermatan sulphates were evaluated were not included. The survey of the literature included a computer-aided *MEDLINE* search from 1980 to 1991, a search of the reference lists of relevant papers by two of the authors (L.N.J., P.W.-J.) independently, and a contemporary computer-aided search of *Current Contents* (field: *Clinical Practice and Life Sciences*) until the end of 1991. The following keywords were used: low molecular weight heparin, heparin, deep venous thrombosis, thromboembolism, pulmonary embolism, surgery and orthopaedic surgery. When data were missing from published reports, the authors responsible for correspondence were contacted. If no answer was received, a reminder was sent after 1 month. If the data were still not forthcoming, the study was excluded

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Table 1 *Definition of high-quality studies (all criteria must be met)*

DVT diagnosis
  Orthopaedic surgery
    1. Venography
    2. ^{125}I-radiolabelled fibrinogen uptake test with or without impedance plethysmography, or plasmin scintimetry if positive results are verified with venography for all the tests
  General or gynaecological surgery
    1. Venography
    2. ^{125}I-radiolabelled fibrinogen uptake test
Follow-up
  ≥7 days for regular DVT screening and ≥30 days for verification of symptomatic DVT, symptomatic pulmonary embolism or death
Completion of trial
  1. No or limited selection of patients
  2. <15% of patients drop out after inclusion
Bleeding and transfusion
  Complete data on amount and type of bleeding, and transfusion requirements

DVT, deep vein thrombosis

from the respective statistical calculations, but still reported. Also excluded from the analysis were dose-finding studies without a control group given another prophylactic treatment for comparison.

The efficacy endpoints assessed were the objectively verified incidences of DVT and pulmonary embolism. Only controlled trials using objective paraclinical diagnostic methods, such as venography, ^{125}I-radiolabelled fibrinogen uptake test, plethysmography, ^{99}Tc-radiolabelled plasmin scintimetry and thermography for the detection of DVT, and pulmonary scintigraphy, pulmonary angiography and autopsy for the verification of pulmonary embolism, were included; the authors are aware that not all of these tests are adequate for diagnosis. The incidence of DVT was based on results of venography in all the studies that applied this method to a majority of patients for the verification of DVT (after initial detection by screening with another objective diagnostic method). In a substantial proportion of studies, separation of results into proximal and distal DVT was not presented; for this reason the total incidence of DVT has been considered. Whenever the relevant data were provided, the incidences of DVT, pulmonary embolism and death were derived from the complete period of follow-up, not just that of thromboprophylaxis or hospital stay. The incidence of DVT was based on patients completing the trial protocol. Whenever possible, data describing the incidences of postoperative pulmonary embolism, postoperative mortality, bleeding complications and transfusion requirements were derived from all patients randomized in the respective trials (i.e. analysis on an intention to treat basis). This was done to avoid the bias that occurs in certain trials from excluding patients because of severe bleeding episodes or death before completion of the trial.

Side-effects such as bleeding complications and requirement for transfusion were not uniformly recorded in the different trials. The studies were scrutinized for significant differences in the total amount of bleeding and transfusions given, irrespective of the time after operation. Bleeding complications included intracranial and gastrointestinal episodes, wound haematoma and significantly raised total blood loss (perioperative and postoperative, including volume in drains). Injection haematomas were not considered in the analysis. A distinction was made between statistically significant differences and tendencies between treatment groups. Whenever there was a significant indication of (1) a higher incidence of life-threatening bleeding episodes, (2) wound haematoma requiring evacuation or (3) discontinuation of prophylaxis because of bleeding, differences between the groups were considered clinically relevant. Transfusion was expressed as the total sum (calculated as the number of units of erythrocyte-containing blood products transfused) given during the period of prophylaxis.

In some analyses relating to diagnostic methods, duration of follow-up and drop-out rate (*Table 1*), a separation was made into two classes of scientific quality (high and low). When different studies had uniform selection of patients and dose regimen, some results were evaluated by combining the data in 2 × 2 tables (Mantel–Haentszel–Peto[2,12,13] method); this allows comparison across studies to obtain an overview of the efficacy and safety of LMWHs compared with different control treatments. Only results from trials with uniformity in the selection of patients and dose regimen were analysed in this way. For each study, the number of observed events (O) (DVT or pulmonary embolism) in patients treated with LMWH was compared with the number expected (E) if the treatment had an effect that was identical with that in the control group. With reference to the variance (Var) of each trial, the differences ($O-E$) were summed and a χ^2 test applied to evaluate whether the number of observed events differed significantly from the number expected if the treatments did not differ. Two-tailed analyses were used, irrespective of the fact that one-tailed statistics had been employed in some publications. Typical odds ratios derived from $\exp[\Sigma\,(O-E)/\Sigma\,\mathrm{Var}(O-E)]$, with the 95 per cent confidence interval derived from $\exp[\Sigma\,(O-E)/\Sigma\,\mathrm{Var}(O-E)] \pm 1{\cdot}96/\Sigma\,\mathrm{Var}(O-E)^{1/2}$, are presented[2].

Tests for heterogeneity have not been performed, since these lack statistical power and a certain degree of heterogeneity is always present[2,14]. Instead, heterogeneity has been evaluated from the graphical presentation of the odds ratios for each trial. The overall typical odds ratios are presented in this form only when derived from studies of similar design using identical pharmaceutical products.

In the evaluation of the prophylactic effect on DVT, each drug was tested separately against each main group of controls: placebo, dextran and unfractionated heparin. Three patient populations were assessed, undergoing: elective major orthopaedic operations, hip fracture surgery, and general surgery including abdominal, thoracic, vascular, urological and gynaecological procedures. Studies in which the dose of the respective LMWH tested differed considerably from the recommendations of the manufacturer were excluded from the analysis. No regard was made to supplementary prophylactic treatment (e.g. compression stockings or DHE) if it was used in both the LMWH-treated and control groups. Two sets of analyses were carried out: the first included all studies irrespective of quality and the second evaluated only high-quality investigations. The same methods were applied when the effects on the incidence of pulmonary embolism and death were examined.

Results

Orthopaedic surgery

Reports of 27 investigations were found. In most trials, patients undergoing elective hip arthroplasty or hip fracture surgery were studied. Without prophylaxis these patients are considered to carry a risk of DVT of approximately 50 per cent, and a risk of pulmonary embolism and fatal pulmonary embolism of 1–2 per cent and 2–10 per cent respectively[15].

Controls receiving placebo. Compared with placebo, three LMWHs have in separate trials proved to be significantly superior with respect to prophylaxis of DVT in patients undergoing elective hip arthroplasty[3,16], knee arthroplasty or tibial osteotomy[17], or repair of femoral neck fracture[18] (*Table 2*). Although not all the trials show significant differences, the individual odds ratios all point towards a thromboprophylactic effect of the LMWH that is better than that of placebo, irrespective of the quality rating (*Figure 1*). In two studies[3,19] the LMWH was supplemented with DHE; graded compression stockings were used in both treatment groups in one trial[20]. In all studies reporting the incidence of proximal DVT, a reduction was found in the active treatment group[3,16,17,20]; this was statistically significant in three[3,16,17].

Table 2 *Low molecular weight heparin* versus *placebo in orthopaedic surgery*

Reference	Follow-up (days)	Surgery	Control group	LMWH (anti-Xa units)	Diagnostic method	Incidence of DVT		Bleeding complications	Transfusion requirements	Incidence of pulmonary embolism‡		Mortality	
						Controls	LMWH			Controls	LMWH	Controls	LMWH
Leclerc *et al.*[17]	42	Knee arthroplasty	Placebo	Clexane 2400 × 2†	FUT plus IPG plus venography	35 of 54	9 of 41*	0	0	1 of 65	1 of 66	0 of 65	1 of 66
Turpie *et al.*[16]	14	Elective hip arthroplasty	Placebo	Clexane 2400 × 2†	FUT plus IPG plus venography	21 of 50	6 of 50*	0	0	0 of 50	0 of 50	1 of 50	0 of 50
Jørgensen *et al.*[18]	42	Fractured hip repair	Placebo	Fragmin 5000 × 1‡	FUT/venography	18 of 34	5 of 26*	0(+)	+	1 of 38 (fatal)	0 of 30	4 of 38	3 of 30
Tørholm *et al.*[22]	42	Elective hip arthroplasty	Placebo	Fragmin 5000 × 1‡	FUT/venography	16 of 51	8 of 57	0	0	1 of 54	0 of 58	0 of 54	0 of 58
Lassen *et al.*[20]	9	Elective hip arthroplasty	Placebo plus compression stockings	Logiparin 50/kg × 1 plus compression stockings	Venography	44 of 97	29 of 93	0(+)	+	1 of 104	1 of 105	1 of 104	1 of 105
Lassen *et al.*[3]	6	Elective hip arthroplasty	Placebo	Sandoparin 4800 plus DHE × 1	Plasmin scintigraphy/venography	53 of 97	35 of 107*	0	0(+)	0 of 116	0 of 118	0 of 116	0 of 118
Lassen *et al.*[19]	6§	Fractured hip repair	Placebo	Sandoparin 4800 plus DHE × 1	Plasmin scintigraphy/venography	23 of 54	14 of 53	0	0	2 of 74 (2 fatal)	1 of 68	3 of 74	4 of 68
Total													
		Elective hip or knee arthroplasty				169 of 349 (48·4%)	87 of 348 (25·0%)			3 of 389 (0·8%)	2 of 397 (0·5%)	2 of 389 (0·5%)	2 of 397 (0·5%)
		Fractured hip repair				41 of 88 (47%)	19 of 79 (24%)			3 of 112 (2·7%; 3 fatal)	1 of 98 (1%)	7 of 112 (6·2%)	7 of 98 (7%)

Knee arthroplasty includes tibial osteotomy. LMWH, low molecular weight heparin; DHE, supplementary treatment with dihydroergotamine 0·5 mg; FUT, ^{125}I-radiolabelled fibrinogen uptake test; FUT/venography, screening with FUT, if positive venography is performed, plasmin scintigraphy/venography, screening with plasmin scintigraphy, if positive venography is performed; IPG, impedance plethysmography; DVT, deep vein thrombosis; 0, no statistically significant difference; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *$P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose given after surgery; ‡first dose (2500 units) 2 h before surgery, second dose (2500 units) 12 h after operation; if nothing is specified, the first dose is given 1–2 h before operation. §Follow-up of mortality 30 days; ‡only symptomatic cases objectively verified

Table 3 *Low molecular weight heparin* versus *dextran in orthopaedic surgery*

Reference	Follow-up (days)	Surgery	Control group	LMWH (anti-Xa units)	Diagnostic method	Incidence of DVT		Bleeding complications	Transfusion requirements	Incidence of pulmonary embolism‡		Mortality	
						Controls	LMWH			Controls	LMWH	Controls	LMWH
DESG[23]	30	Elective hip arthroplasty	Dextran	Clexane 3200 × 1†	Venography	27 of 111	7 of 108*	–	0(–)	0 of 126	0 of 120	0 of 126	1 of 120
Eriksson *et al.*[24]	42	Elective hip arthroplasty	Dextran	Fragmin 2500 × 2	Venography	22 of 49	10 of 49*	–	–	2 of 50	2 of 50	0 of 50	0 of 50
Matzsch *et al.*[25]	30	Elective hip arthroplasty	Dextran	Logiparin 35/kg × 1	FUT/venography	11 of 42	9 of 45	0(–)	0	0 of 49	0 of 47	0 of 49	0 of 47
Mätzsch *et al.*[26]	30	Elective hip arthroplasty	Dextran	Logiparin 50/kg × 1	FUT/venography	32 of 108	21 of 111	0(–)	0	0 of 123	2 of 120	1 of 123	1 of 120
Total						92 of 310 (29·7%)	47 of 313 (15·0%)			2 of 348 (0·6%)	4 of 337 (1·2%)	1 of 348 (0·3%)	2 of 337 (0·6%)

LMWH, low molecular weight heparin; DVT, deep vein thrombosis; FUT/venography, screening with ^{125}I-radiolabelled fibrinogen uptake test, if positive venography is performed; 0, no statistically significant difference, –, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *$P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose given 12 h before surgery; if nothing is specified, the first dose is given 1–2 h before operation; ‡only symptomatic cases objectively verified

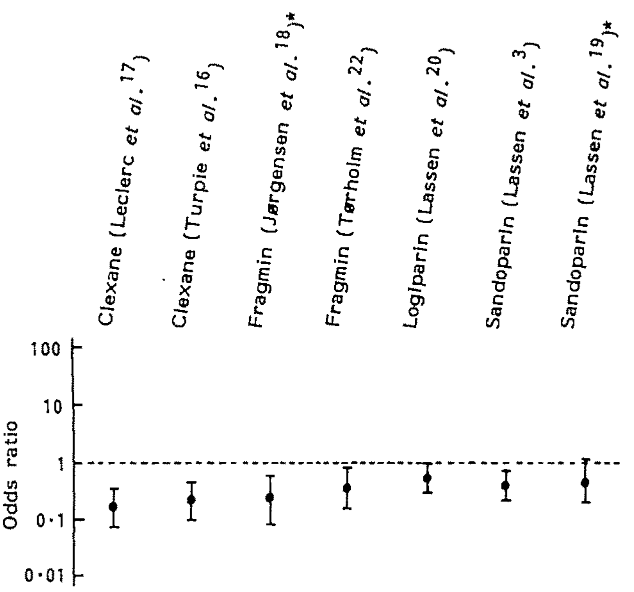

Figure 1 *Prophylactic effect of low molecular weight heparins (with or without dihydroergotamine)* versus *placebo with respect to deep vein thrombosis in orthopaedic surgery. Bars are 95 per cent confidence intervals. * Hip fracture surgery*

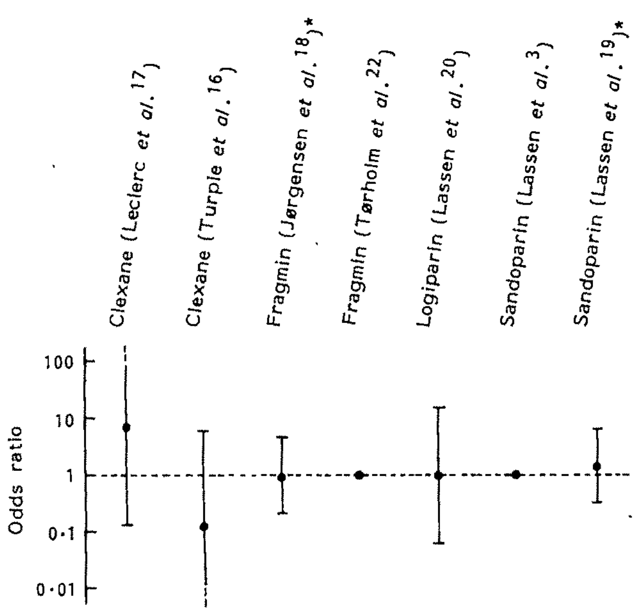

Figure 2 *Prophylactic effect of low molecular weight heparins (with or without dihydroergotamine)* versus *placebo with respect to mortality rate in orthopaedic surgery. Bars are 95 per cent confidence intervals. * Hip fracture surgery*

It is worth noting that in two trials the prophylactic treatment was initiated after surgery[16,17]. To the authors' knowledge these studies, including that of Levine and colleagues[21], are the only reports on postponing the start of LMWH prophylaxis until after surgery.

With respect to the incidence of pulmonary embolism, no overall tendency was detected between the groups when patients undergoing elective surgery were analysed[3,16,17,20,22]; however, the three cases of fatal pulmonary embolism were confined to the placebo-treated group in the two hip fracture studies[18,19] (*Table 2*).

When mortality was evaluated, great heterogeneity between the trials was obvious and no overall tendency shown (*Figure 2*). For this reason, meta-analysis was omitted.

In only one study was there a significantly higher operative blood loss in patients receiving LMWH compared with that in the placebo-treated group[3] (*Table 2*). Two other trials reported a non-significantly higher incidence of bleeding complications in the LMWH-treated group, which did not lead to discontinuation of prophylaxis for any patient[18,20]. Similarly, transfusion requirements were slightly higher in the group receiving active treatment in these studies.

Controls receiving dextran. Three LMWHs have been compared with dextran in patients undergoing hip arthroplasty[23–26] (*Table 3*). The administration of Clexane, Fragmin and Logiparin caused a reduction in the incidence of DVT, which was statistically significant for Clexane and Fragmin (*Figure 3*). In one investigation[25] only a limited reduction was found (odds ratio 0·71), which may be related to use of an insufficient dose of Logiparin (35 rather than the recommended 50 antifactor Xa units/kg daily). The incidence of proximal DVT was not significantly lowered in any trial.

There were only a few pulmonary embolisms and deaths, and no indication of a reduced incidence of either in LMWH-treated patients. In two of the studies[23,24] the amount of bleeding was found to be significantly higher in patients given dextran.

Controls receiving unfractionated heparin with or without dihydroergotamine. The antithrombotic efficacy of LMWHs compared with unfractionated heparin has been evaluated in 18 trials (*Table 4*), mostly on patients undergoing elective hip arthroplasty. Overall, LMWHs exhibited an effect on the incidence of DVT at least as great as that of unfractionated heparin. Indeed, in 11 of 14 hip arthroplasty trials the odds ratio was $< 1 \cdot 0$, favouring the use of LMWHs (*Figure 4*). When a meta-analysis of the results from the two high-quality studies comparing Clexane with unfractionated heparin 15 000 units per day was performed, a significant reduction in the DVT rate was found in patients treated with Clexane (odds ratio 0·67 (95 per cent confidence interval (c.i.) 0·47–0·96)). Treatment of the control group in the Fragmin studies was not homogeneous, making stratification necessary. The typical odds ratio (95 per cent c.i.) for the trials of Fragmin against unfractionated heparin 5000 units subcutaneously three times daily was 0·54 (0·27–1·11)[31,32] and 0·65 (0·27–1·57) (both P not significant) for studies with controls receiving unfractionated heparin 5000 units plus DHE 0·5 mg subcutaneously twice daily[33,34]. Thus, there is evidence that Fragmin is at least as efficient as these conventional prophylactic regimens.

Compared with unfractionated heparin–DHE, Fragmin appears to be at least as antithrombotic[33,34] (*Table 4*). The

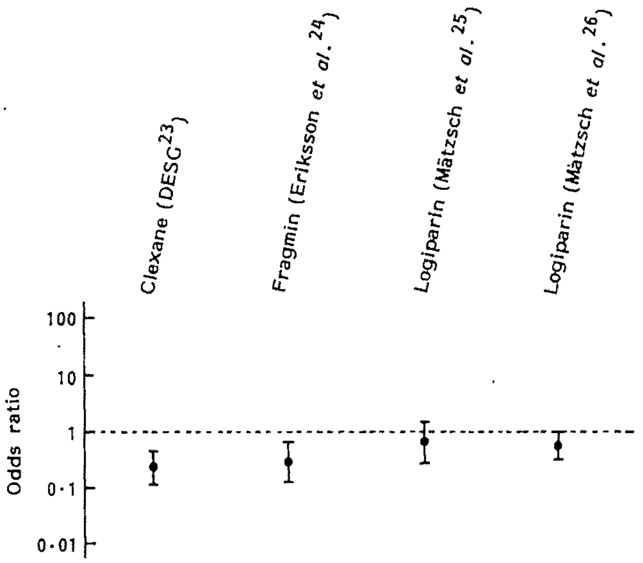

Figure 3 *Effect of low molecular weight heparins* versus *dextran on the incidence of deep vein thrombosis in elective hip arthroplasty. Bars are 95 per cent confidence intervals*

Table 4 *Low molecular weight heparin* versus *low-dose unfractionated heparin in orthopaedic surgery*

						Incidence of DVT				Incidence of pulmonary embolism‡‡		Mortality	
Reference	Follow-up (days)	Surgery	Control group (units unfractionated heparin)	LMWH (anti-Xa units)	Diagnostic method	Controls	LMWH	Bleeding complications	Transfusion requirements	Controls	LMWH	Controls	LMWH
Levine *et al.*[21]	10	Elective hip arthroplasty	7500 × 2	Clexane 2400 × 2†	FUT plus IPG plus venography	61 of 263	50 of 258	0(−)	0	2 of 332	0 of 333	0 of 332	0 of 333
Planes *et al.*[38]	12	Elective hip arthroplasty	5000 × 3	Clexane 3200 × 1#	Venography	27 of 108	15 of 120*	0(+)	−	1 of 113	0 of 124	0 of 113	0 of 124
Chiapuzzo *et al.*[27]	?	Various orthopaedic procedures	5000 × 3	Fluxum 2500 × 2	Doppler	7 of 70	5 of 70	?	?	0 of 70	0 of 70	?	?
Pini *et al.*[28]	14	Fractured hip repair	5000 × 3	Fluxum 2500 × 2	FUT plus IPG/venography	7 of 24	5 of 25	0	0	1 of 24	0 of 25	2 of 24	0 of 25
Barre *et al.*[29]	60	Elective hip arthroplasty	Adjusted dose	Fragmin 2500 × 2§	Venography	4 of 40	7 of 40	0	0(−)	0 of 40	0 of 40	0 of 40	1 of 40
Binsack *et al.*[31]	?	Elective hip arthroplasty	5000 × 3	Fragmin 5000 × 1§	FUT/venography	2 of 41	0 of 34	0	?	?	?	?	?
Breyer *et al.*[33]	42	Various orthopaedic procedures	5000 plus DHE × 2	Fragmin 5000 × 1§	FUT	6 of 60	3 of 60	0	0	0 of 60	0 of 60	0 of 60	0 of 60
Dechavanne *et al.*[30]	10	Elective hip arthroplasty	Adjusted dose	Fragmin 5000 × 1§ Fragmin 2500 × 2§	FUT plus venography	4 of 38	3 of 39 2 of 38	0 0	0 0	0 of 40	0 of 41 0 of 41	0 of 40	0 of 41 0 of 41
Eriksson *et al.*[32]	42	Elective hip arthroplasty	5000 × 3	Fragmin 5000 × 1#	Venography	25 of 59	19 of 63	− (clinical)	− (clinical)	2 of 69	1 of 67	1 of 69	0 of 67
Haas *et al.*[34]	7	Elective hip arthroplasty	5000 plus DHE × 2	Fragmin 5000 × 1§	FUT	7 of 48	6 of 50	0	+ (clinical)	0 of 55	0 of 55	?	?
Monreal *et al.*[41]	8	Fractured hip repair	5000 × 3	Fragmin 5000 × 1‡	Clinical/venography	Excluded from analysis		0(+)	+	Excluded from analysis (screening for embolism)		3 of 44	2 of 46
GHAT Group[39]	42	Elective hip arthroplasty	5000 × 3 plus compression stockings	Fraxiparin 3300 × 1# plus compression stockings	Venography	43 of 137	35 of 136**	0	0	6 of 168 (2 fatal)	2 of 167	3 of 168	0 of 167
Leyvraz *et al.*[40]	30	Elective hip arthroplasty	Adjusted dose	Fraxiparin 33 50/kg × 1†¶	Venography	28 of 175	22 of 174	0(−)	0	6 of 204 (1 fatal)	1 of 205	2 of 204	1 of 205
Freick and Haas[36]	10	Elective hip arthroplasty	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Venography plus Doppler	12 of 48	5 of 52	0(−)	0	1 of 55	0 of 55	0 of 55	0 of 55
Haas *et al.*[35]	7	Elective hip arthroplasty	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT	15 of 73	15 of 73	0(+)	+	1 of 80	0 of 80	0 of 80	0 of 80
Korninger *et al.*[37]	14	Fractured hip repair	5000 × 3 plus acenocoumarol	Sandoparin 4800 × 2	FUT/venography	7 of 33	3 of 35	0	0	1 of 33 (fatal)	0 of 35	1 of 33	0 of 35
Lassen *et al.*[3]	6	Elective hip arthroplasty	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Plasmin scintigraphy/ venography	34 of 112	35 of 107	0	0(+)	0 of 122	0 of 118	0 of 122	0 of 118
Lassen *et al.*[19]	6††	Fractured hip repair	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Plasmin scintigraphy/ venography	23 of 54	14 of 53	0	0	0 of 71	1 of 68	2 of 71	4 of 68
Total													
		Elective hip arthroplasty plus various orthopaedic procedures				275 of 1272 (21·62%)	222 of 1314 (16·89%)			19 of 1408 (1·35%; 3 fatal)	4 of 1456 (0·27%)	6 of 1283 (0·47%)	2 of 1331 (0·15%)
		Fractured hip repair				37 of 111 (33·3%)	22 of 113 (19·5%)			2 of 128 (1·6%; 1 fatal)	1 of 128 (0·8%)	8 of 172 (4·7%)	6 of 174 (3·5%)

Various orthopaedic procedures excludes hip fracture repair. LMWH, low molecular weight heparin; DHE, supplementary treatment with dihydroergotamine 0·5 mg; DVT, deep vein thrombosis; FUT/venography, screening with ^{125}I-radiolabelled fibrinogen uptake test, if positive venography is performed; IPG, impedance plethysmography; 0, no statistically significant difference in bleeding or transfusion requirements; −, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *$P < 0·05$ (control *versus* LMWH, χ^2 test); †first dose given 12 h after surgery; ‡first dose (2500 units) given 2 h before surgery; §first dose (2500 units) given 2 h before surgery, second dose (2500 units) 12 h after operation; #first dose given 12 h before surgery, second dose 12 h after operation; ¶42 units per kg per day until day 3, 62 units per kg per day for days 4–10; if nothing is specified, the first dose is given 1 2 h before operation. **, excluding thrombosis confined solely to the muscle veins; ††follow-up of mortality 30 days; ‡‡only symptomatic cases objectively verified

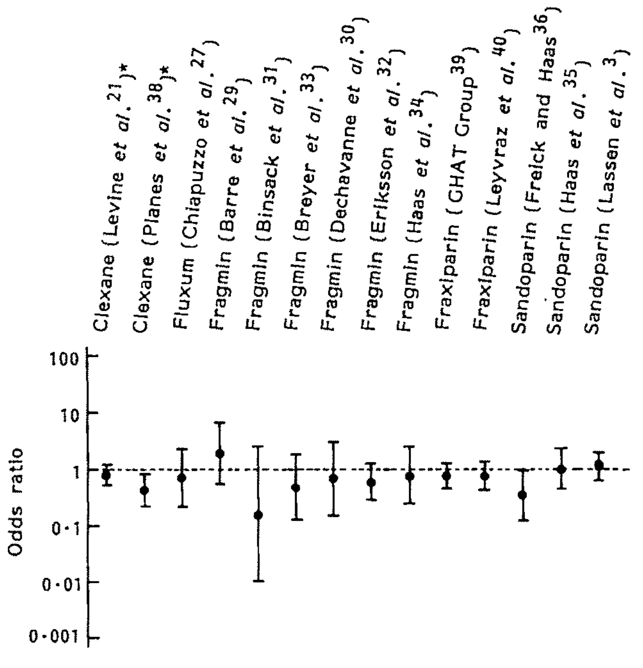

Figure 4 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without dihydroergotamine) on the incidence of deep vein thrombosis in elective hip arthroplasty. Bars are 95 per cent confidence intervals. *Typical odds ratio 0·67 (95 per cent confidence interval 0·47–0·96)* (P < *0·05*)

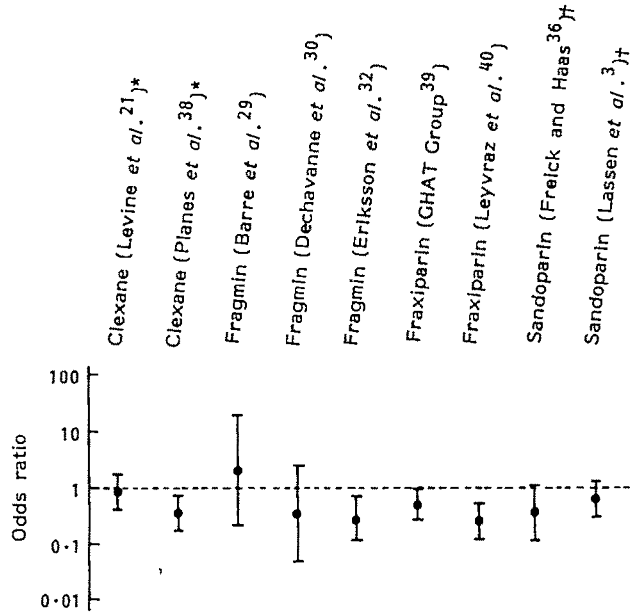

Figure 5 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without dihydroergotamine) on the incidence of proximal deep vein thrombosis in elective hip arthroplasty. Bars are 95 per cent confidence intervals. Typical odds ratio (95 per cent confidence interval): *0·57 (0·34–0·97)* (P < *0·05*)*; †0·51 (0·28–0·94)* (P < *0·05*)

efficacy of a combination of Sandoparin and DHE compared with unfractionated heparin–DHE has been investigated in four trials[3,19,35,36] (*Table 4*). A meta-analysis performed on the three studies of patients undergoing elective hip arthroplasty showed no significant difference in antithrombotic effect between the two regimens (odds ratio 0·89 (95 per cent c.i. 0·58–1·36)). Similar results were found in patients undergoing hip fracture surgery[19]. Prophylaxis of postoperative DVT using Sandoparin 4800 units combined with DHE 0·5 mg subcutaneously once daily appears at least as effective as that with unfractionated heparin 5000 units plus DHE 0·5 mg subcutaneously twice daily. In one study of patients with hip fracture the thromboprophylactic action of Sandoparin was tested against that of unfractionated heparin followed by the administration of a vitamin K antagonist; no significant difference was found between the groups[37].

In eight of the nine trials reporting on the incidence of proximal DVT the odds ratio was <1·0, again in favour of LMWHs (*Figure 5*). The typical odds ratio (95 per cent c.i.) for the Clexane studies[21,38] was 0·57 (0·34–0·97) ($P < 0·05$) and for the two Sandoparin studies[3,36] 0·51 (0·28–0·94) ($P < 0·05$).

Except for the reports of Eriksson *et al.*[32] and Monreal and colleagues[41], no regular screening for pulmonary embolism was performed in any trial. From 13 elective hip trials comparing LMWHs and unfractionated heparin, the incidence of pulmonary embolism could be obtained (*Table 4*). The results favour the LMWHs, as seven studies showed a higher incidence in the control group (odds ratio <1) and none a higher incidence of pulmonary embolism in LMWH-treated patients (odds ratio >1) (*Figure 6*). In all the orthopaedic trials reviewed, reporting the results from 4615 patients, fatal pulmonary embolism was reported in seven cases (0·15 per cent)[18,19,37,39,40], four of whom underwent femoral neck repair. No patient with fatal pulmonary embolism was treated with LMWH prophylaxis. Eleven cases of pulmonary embolism (0·49 per cent) were reported in 2230 patients receiving LMWH compared with 23 (1·22 per cent) of 1884 controls receiving either unfractionated heparin, unfractionated heparin–DHE, dextran or unfractionated heparin–vitamin K antagonists. The number of deaths was too small to permit comparison between groups.

With respect to the rate of bleeding complications, no overall reproducible difference was found between groups. This was also the case when the data were analysed for each compound. In one investigation comparing Fragmin with unfractionated heparin, significantly less bleeding was observed in patients receiving the LMWH[32]. The dose regimen was unique, as prophylaxis was started 12 h before surgery instead of 2 h.

No obvious pattern was detected when transfusion require-

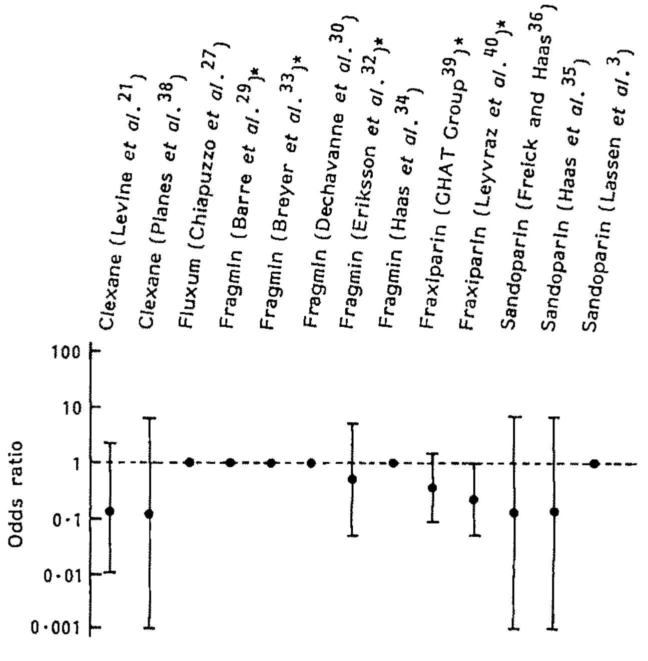

Figure 6 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without dihydroergotamine) on the incidence of pulmonary embolism in elective hip arthroplasty. Bars are 95 per cent confidence intervals. *At least 30 days' follow-up*

Table 5 *Low molecular weight heparin* versus *placebo in general surgery*

Reference	Follow-up (days)	Control group	LMWH (anti-Xa units)	Diagnostic method	Incidence of DVT		Bleeding complications	Transfusion requirements	Incidence of pulmonary embolism‡		Mortality	
					Controls	LMWH			Controls	LMWH	Controls	LMWH
Valle *et al.*[43]	?	Placebo	Fluxum 2500 × 1	Doppler	3 of 50	0 of 50	0	0	0 of 50	0 of 50	?	?
Ockelford *et al.*[42]	42	Placebo	Fragmin 2500 × 1	FUT	14 of 88	4 of 95	0	0(+)	2 of 97	0 of 102	2 of 97	1 of 102
Pezzuoli *et al.*[44]	?	Placebo	Fraxiparin 2500 × 1*	?	?	?	+	+	4 fatal of 2251	2 fatal of 2247†	18 of 2251	8 of 2247
Total					17 of 138 (12·3%)	4 of 145 (2·8%)			2 of 147 (1·4%) (4 fatal of 2398; 0·17%)	0 of 152 (0·0%) (2 fatal of 2399; 0·08%)	20 of 2348 (0·85%)	9 of 2349 (0·38%)

LMWH, low molecular weight heparin; DVT, deep vein thrombosis; FUT, ^{125}I-radiolabelled fibrinogen uptake test; 0, no statistically significant difference in bleeding or transfusion requirements; −, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *On day of operation 7500 units given 2 h before surgery and 7500 units 12 h after first injection; if nothing is specified, the first dose is given 1–2 h before operation. †Fatal pulmonary embolism assessed; ‡only symptomatic cases. Patients not fully completing the trial included; incidence for the whole follow-up

ments in each treatment group were analysed (*Table 4*). Clinically relevant differences were observed in only two trials. Eriksson and co-workers[32] reported that Fragmin- and unfractionated heparin-treated patients required a mean of 2·3 and 3·3 red cell units respectively, whereas Haas and colleagues[34] found the opposite effect. The regimens tested were, however, not identical.

General and gynaecological surgery

Controls receiving placebo. Of the three studies available, regular screening for DVT with an acceptable method was carried out only by Ockelford and co-workers[42] (*Table 5*). Prophylactic treatment with Fragmin 2500 units subcutaneously once daily reduced the rate of DVT diagnosed by the fibrinogen uptake test from 17·0 per cent (95 per cent c.i. 10·7–25·0 per cent) to 4·2 per cent (95 per cent c.i. 1·4–9·5 per cent) ($P < 0·01$). There was no difference in the bleeding tendency. Fatal pulmonary embolism was assessed as the endpoint in a large-scale assessor-blind study randomizing 4498 patients to treatment with placebo or Fraxiparin 2500 units once daily[44]. Four patients in the placebo-treated group and two receiving LMWH died from pulmonary embolism. The total mortality rate was reduced from 0·80 to 0·36 per cent.

Controls receiving unfractionated heparin with or without dihydroergotamine. The prophylactic use of low-dose unfractionated heparin has been intensively studied. With this treatment the incidence of DVT, pulmonary embolism and fatal pulmonary embolism is approximately 10, 0·5 and 0·2 per cent respectively[45]. Most trials in which the prophylactic effect of LMWHs was investigated were conducted using unfractionated heparin for controls. From 32 studies, 38 comparisons between LMWHs and unfractionated heparin have been published, with supplementary DHE administered to both treatment groups in six investigations[46–51] and exclusively to the unfractionated heparin-treated group in one[52] (*Table 6*). In all studies, the incidence of DVT was the endpoint. The diagnostic method most often used was the fibrinogen uptake test, sometimes with verification by venography. A significant reduction in the incidence of DVT by administration of a LMWH was obtained in three studies. The treatment regimens were Fragmin 5000 units subcutaneously once daily, Fraxiparin 2500 units subcutaneously once daily and Sandoparin 8000 units plus DHE 0·5 mg subcutaneously once daily[47,56,57] and the respective odds ratios (95 per cent c.i.) 0·53 (0·31–0·90), 0·26 (0·10–0·69) and 0·31 (0·12–0·82).

The odds ratios for all the trials were $<1·0$ in 15, 1·0 in nine and $>1·0$ in six; these generally favour the use of LMWHs (*Figure 7*). If only the high-quality studies are included, the corresponding numbers of trials with these odds ratios are four, three and three, with some of the largest studies[56,58–60] belonging to the group favouring LMWHs. Many of the Fragmin studies were not homogeneous and so do not allow proper meta-analysis. This is so even after stratification with respect to dose regimens in the LMWH-treated and control groups of patients. Three studies compared unfractionated heparin 5000 units subcutaneously three times daily with Sandoparin 4800 units subcutaneously once daily[60–62], for which a typical odds ratio of 0·73 (95 per cent c.i. 0·44–1·23) was found, a non-significant reduction in the DVT rate in Sandoparin-treated patients.

The total incidence of symptomatic pulmonary embolism reported for patients receiving LMWH and unfractionated heparin was 0·16 per cent (fatal embolism 0·02 per cent) and 0·60 per cent (fatal embolism 0·13 per cent) respectively (*Table 6*). In none of the studies was regular screening for pulmonary embolism performed. Data on the incidence of pulmonary embolism could be obtained in 27 of the 32 published studies, often only by direct communication with the authors. As the number of observations of pulmonary embolism in each trial was small, the confidence intervals for each odds

Table 6 *Low molecular weight heparin* versus *low-dose unfractionated heparin in general and gynaecological surgery*

Reference	Follow-up (days)	Surgery	Control group (units unfractionated heparin)	LMWH (anti-Xa units)	Diagnostic method	Incidence of DVT		Bleeding complications	Transfusion requirements	Incidence of pulmonary embolism**		Mortality	
						Controls	LMWH			Controls	LMWH	Controls	LMWH
Samama *et al.*[72]	7	General	5000 × 3 5000 × 3 5000 × 3	Clexane 1600 × 1 Clexane 3200 × 1 Clexane 4800 × 1	FUT FUT FUT	12 of 158 3 of 110 5 of 133	6 of 159 3 of 106¶ 4 of 137¶	0(−) 0 0	0(+) 0(−) 0	0 of 167 0 of 123 1 of 147	0 of 167 0 of 124¶ 0 of 157¶	0 of 167 0 of 123 0 of 147	1 of 167 1 of 124¶ 2 of 157¶
Catania and Salanitri[53]	?	General	5000 × 2	Fluxum 2500 × 1	Doppler	6 of 85	1 of 88	0(−)	0(−)	0 of 85	0 of 88	3 of 85	2 of 88
Corrado *et al.*[71]	?	Urological	5000 × 2	Fluxum 5000 × 1	FUT	3 of 29	3 of 29	0	?	0 of 29	0 of 29	?	?
Speziale *et al.*[68]	?	Vascular	5000 × 2	Fluxum 5000 × 1	FUT/Doppler	4 of 46	3 of 46	0	?	?	?	?	?
Verardi *et al*[70]	8	General	5000 × 2	Fluxum 5000 × 1	FUT/Doppler	3 of 44	1 of 44	0(−)	?	?	?	?	?
Verardi *et al.*[69]	7	General	5000 × 2 5000 × 3	Fluxum 2500 × 1 Fluxum 5000 × 1	FUT/Doppler or plethysmography	7 of 134 12 of 168	9 of 250 1 of 58	0(−) 0(−)	0(−) 0(−)	0 of 134 3 of 168	1 of 250 0 of 58	? ?	? ?
Bergqvist *et al.*[63]	30	General	5000 × 2	Fragmin 5000 × 1	FUT	10 of 192	13 of 190	+ (clinical)	0(+)	1 of 217	0 of 215	5 of 217	5 of 215
Bergqvist *et al.*[56]	30	General	5000 × 2	Fragmin 5000 × 1†	FUT	37 of 405	21 of 421*	+	0	5 of 497 (1 fatal)	0 of 505	10 of 497	10 of 505
Borstad *et al*[65]	7	Gynaecological	5000 × 2	Fragmin 5000 × 1	Plethysmography/ venography	0 of 110	0 of 105	+ (clinical)	+ (clinical)	0 of 110	0 of 105	0 of 110	0 of 105
Briel *et al.*[52]	8	Gynaecological	5000 plus DHE × 2	Fragmin 5000 × 1‡	Thermography/ venography	1 of 98	1 of 95	0(+)	0	0 of 98	0 of 95	0 of 98	0 of 95
Caen[59]	30	General/ gynaecological	5000 × 2	Fragmin 2500 × 1	FUT	7 of 190	6 of 195	0	0	1 of 190	0 of 195	3 of 190	4 of 195
Creperio *et al.*[54]	?	General	5000 × 2	Fragmin 2500 × 1	FUT	5 of 20	5 of 20	0	?	?	?	?	?
Fricker *et al.*[64]	30	Gynaecological	5000 × 3	Fragmin 5000 × 1‡	FUT/venography	1 of 40	1 of 40	−	0	5 of 40 (1 fatal)	0 of 40	2 of 40	2 of 40
Hartl *et al.*[77]	30	General	5000 × 2	Fragmin 2500 × 1	FUT/venography	5 of 115	5 of 112	0	−	1 of 124 (fatal)	1 of 126 (fatal)	4 of 124	6 of 126
Koller *et al.*[66]	30	General	5000 × 2 5000 × 2	Fragmin 7500 × 1 Fragmin 2500 × 1	FUT/venography	0 of 20 1 of 68	0 of 23¶ 2 of 70	+ (clinical) 0	+ (clinical) 0(−)	0 of 20 1 of 75	0 of 23¶ 0 of 75	0 of 20 0 of 75	0 of 23¶ 0 of 75
Onarheim *et al.*[55]	30	General	5000 × 2	Fragmin 5000 × 1	FUT/venography	0 of 27	1 of 25	0	0	0 of 27	0 of 25	0 of 27	0 of 25
Barbui *et al.*[74]	?	General	5000 × 2	Fraxiparin 2500 × 1	FUT/venography	2 of 33	2 of 27	−	?	2 of 173	0 of 171	?	?

Dahan *et al.*[13]	7	Thoracic (malignant)	5000 × 2/adjusted dose	Fraxiparin 2500 × 1§	FUT/venography	0 of 41	0 of 46	0(−)	?	0 of 40	0 of 40	?	?
EFSG[58]	30	General	5000 × 3 plus compression stockings	Fraxiparin 2500 × 1☨ plus compression stockings	FUT	42 of 936	27 of 960	0	0	4 of 936 (1 fatal)	1 of 960	12 of 936	10 of 960
Kakkar and Murray[57]	7	General	5000 × 2	Fraxiparin 2500 × 1	FUT	14 of 174	3 of 172*	0	0(+)	1 of 199 (fatal)	0 of 196	6 of 199	5 of 196
Leizorovicz *et al.*[75]	30	General	5000 × 2	Logiparin 3500 × 1 Logiparin 2500 × 1	FUT/venography	7 of 429	7 of 430 16 of 431¶	0 0(−)	0 0	2 of 429	1 of 430 4 of 431¶	9 of 429	10 of 430 10 of 431¶
Adolf *et al.*[60]	30	General	5000 × 3	Sandoparin 4800 × 1	FUT	22 of 195	21 of 195	0(−)	0(+)	0 of 202	0 of 202	1 of 202	1 of 202
Baumgartner *et al.*[49]	6	General	2500 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT/venography	7 of 89	6 of 87	0	?	1 of 102 (fatal)	1 of 99	2 of 102	1 of 99
Heilmann *et al.*[61]	28	Gynaecological	5000 × 3	Sandoparin 4800 × 1	Plethysmography/ venography	6 of 150	2 of 150	0(−)	0(−)	0 of 150	0 of 150	0 of 150	0 of 150
Hoffmann *et al.*[76]	10	General	5000 × 2	Sandoparin 4800 plus DHE × 1	Clinical	0 of 237¶	0 of 245¶	0(−)	0	0 of 237	0 of 245	0 of 237	0 of 245
Kakkar *et al.*[46]	?	General	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT/venography	10 of 91	8 of 88	0(+)	0(+)	0 of 91	2 of 88	?	?
Koppenhagen *et al.*[62]	?	General	5000 × 3	Sandoparin 4800 × 1	FUT/venography	7 of 53	4 of 51	0(+)	0	?	?	?	?
Sasahara *et al*[48]	7	General	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	FUT/venography	13 of 126	14 of 134	0	−	2 of 132 (1 fatal)	0 of 137	5 of 132	2 of 137
Schmitz-Huebner *et al.*[67]	30	General	5000 × 2 plus compression stockings	Sandoparin 4000 × 2 plus compression stockings Sandoparin 5600 × 2 plus compression stockings	FUT	0 of 39	3 of 40 0 of 41¶	0 +(clinical)	0 0(+)	0 of 42	0 of 41 0 of 43¶	0 of 42	0 of 41 2 of 43¶
Steiner *et al.*[50]	12	Gynaecological	5000 plus DHE × 2/ acenocoumarol	Sandoparin 4800 plus DHE × 1	Clinical/Doppler	1 of 99¶	1 of 92¶	0(+)	?	0 of 99	1 of 92	0 of 99	0 of 92
Voigt *et al.*[51]	7	General	5000 plus DHE × 2	Sandoparin 4800 plus DHE × 1	Clinical/venography	1 of 97¶	1 of 103¶	0	0	1 of 103	0 of 107	6 of 103	4 of 107
Welzel *et al.*[47]	?	General	5000 plus DHE × 2	Sandoparin 8000 plus DHE × 1	FUT	14 of 103	4 of 98*	0	?	?	?	?	?
Total						266 of 4651 (5·72%)	180 of 4425 (4·07%)			31 of 5186 (0·60%; 7 fatal)	8 of 4931 (0·16%; 1 fatal)	68 of 4551 (1·49%)	63 of 4295 (1·47%)

LMWH, low molecular weight heparin, DHE, supplementary treatment with dihydroergotamine 0·5 mg; DVT, deep vein thrombosis; FUT/venography, screening with ^{125}I-radiolabelled fibrinogen uptake test, if positive venography is performed; 0, no statistically significant difference in bleeding or transfusion requirements; −, significantly lower rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group; +, significantly higher rate of bleeding complications or total transfusion (erythrocytes or whole blood) requirements in the LMWH-treated group. *$P < 0.05$ (control *versus* LMWH, χ^2 test); †first dose (5000 units) given 12 h before surgery; ‡first dose (2500 units) given 2 h before surgery, second dose (2500 units) 12 h after first injection; §first dose given 12 h before surgery, on days 3–7 10 000 units once daily; ☨on day of operation 7500 units given 2 h before surgery and 7500 units 8 h after operation; if nothing is specified, the first dose is given 1–2 h before operation. Acenocoumarol was started on day 2 after operation. ¶Excluded from analysis, dose not as recommended by manufacturer or only symptomatic DVT assessed; **only symptomatic cases objectively verified

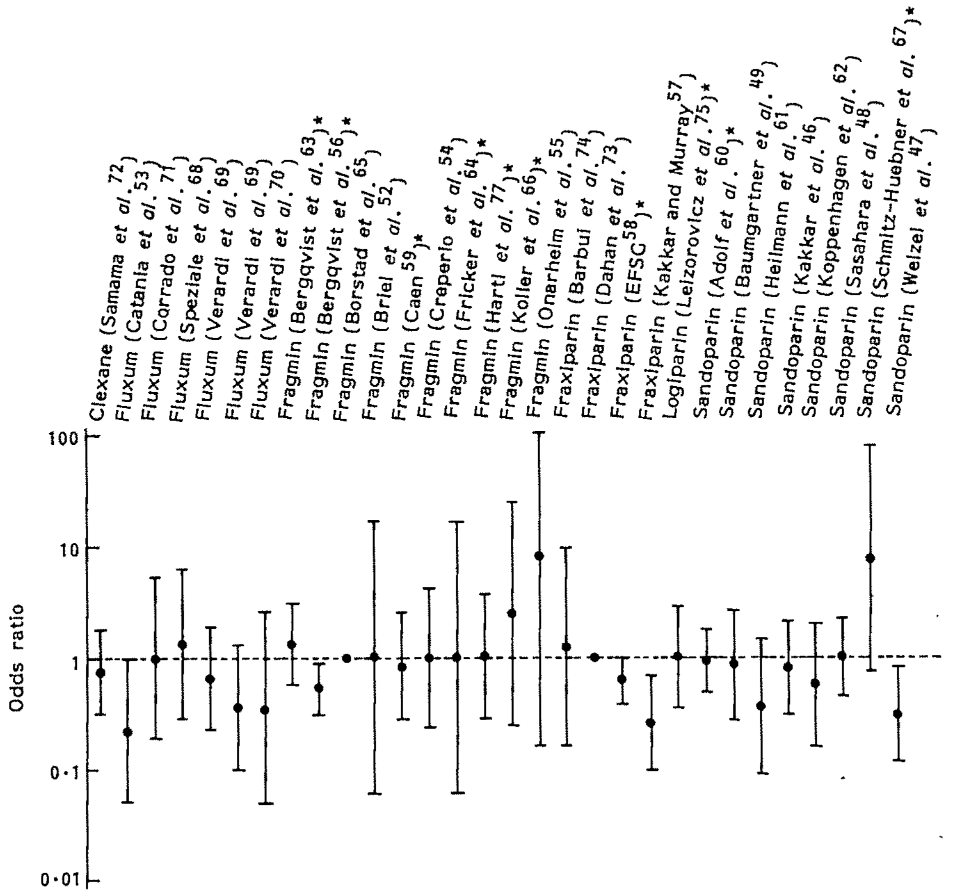

Figure 7 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without dihydroergotamine) on the incidence of deep vein thrombosis in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quality studies*

ratio appear wide, especially if few patients were allocated in the respective trial (*Figure 8*). In 13 studies the odds ratio was < 1·0 (in favour of LMWH), whereas a ratio > 1·0 was observed in only three. In ten investigations no case of pulmonary embolism occurred, leading to an apparent odds ratio of 1·0. If one includes only the high-quality studies, a higher homogeneity appears with no odds ratio > 1·0. There were no cases of pulmonary embolism reported in the three Sandoparin trials. Prophylaxis with Fragmin, Fraxiparin or Logiparin led to a reduced risk of pulmonary embolism although without a clear statistical significance in each single investigation. Meta-analysis of the three high-quality studies[56,63,64], in which the LMWH-treated patients received the high-risk patient dose of Fragmin 5000 units daily, showed a typical odds ratio of 0·13 (95 per cent c.i. 0·04–0·42) ($P < 0{\cdot}01$), suggesting an overall reductive effect on the incidence of postoperative pulmonary embolism of Fragmin compared with that of unfractionated heparin.

There were even fewer cases of postoperative fatal pulmonary embolism; in 21 of 28 trials there were no fatal pulmonary embolisms, leading to an apparent odds ratio of 1·0 in each (*Figure 9*). Again, no trial showed a significant difference between treatment groups. However, there is a weak visual impression of an overall superior prophylactic efficacy of LMWHs over unfractionated heparin. Meta-analysis of the three Fragmin studies mentioned above showed a lower incidence of fatal pulmonary embolism in the Fragmin-treated group that was not statistically significant (typical odds ratio 0·13 (95 per cent c.i. 0·01–2·15)).

With respect to total postoperative mortality, no clear overall difference was found between treatment groups, either for all studies available or for those of high quality (*Figure 10*).

A significantly increased amount of bleeding in LMWH-treated patients was observed in five studies[56,63,65–67] and considered clinically relevant in four (*Table 6*). Different dose regimens related to the prophylactic use of Fragmin have been intensively studied in patients undergoing general surgery. Bergqvist *et al.*[63] found that Fragmin 5000 units daily initiated 2 h before surgery was significantly more haemorrhagic (excessive peroperative bleeding, wound haematomas and number of reoperations for bleeding) than conventional heparin 5000 units twice daily. Similar findings were made by Borstad *et al.*[65] using a similar dose regimen in gynaecological patients. If the time of the first 5000-unit Fragmin dose was advanced to 12 h before surgery, the regimen was still more likely to cause bleeding than the use of unfractionated heparin, but the bleeding episodes were only minor and efficacy was maintained[56]. Another safe and efficient approach[57,64] has been to reduce the dose of Fragmin given 2 h before surgery to 2500 units, repeated after 12 h. Koller *et al.*[66] and Schmitz-Huebner and colleagues[67] used higher LMWH doses than now recommended in some of their studies (Fragmin 7500 units daily, Sandoparin 5600 units twice daily) and experienced a significantly higher number of clinically relevant bleeding complications, leading to interruption of the study of Koller *et al.* Prophylaxis with Fluxum 5000 units once daily[68–71], Clexane 1600 units (20 mg) once daily[72], Fraxiparin 2500 units once daily[57,58,73,74], Logiparin 3500 units once daily[75] or Sandoparin 4800 units (with or without DHE) once daily has proved to be efficient without causing significantly more bleeding than standard low-dose heparin[46,48–51,60–62,76]. It appears, however, that there is no basis for the claim that the prophylactic use of LMWHs as a group causes fewer bleeding complications than that of unfractionated heparin (*Table 6*).

Higher transfusion requirements in Fragmin-treated patients than in those receiving unfractionated heparin were found in two studies[65,66] (*Table 6*) in which Fragmin 5000–7500 units was given 2 h before surgery. Lowering the preoperative dose to 2500 units, but withholding a 5000-unit daily dose in the days after operation, led to the elimination of this tendency[52,64].

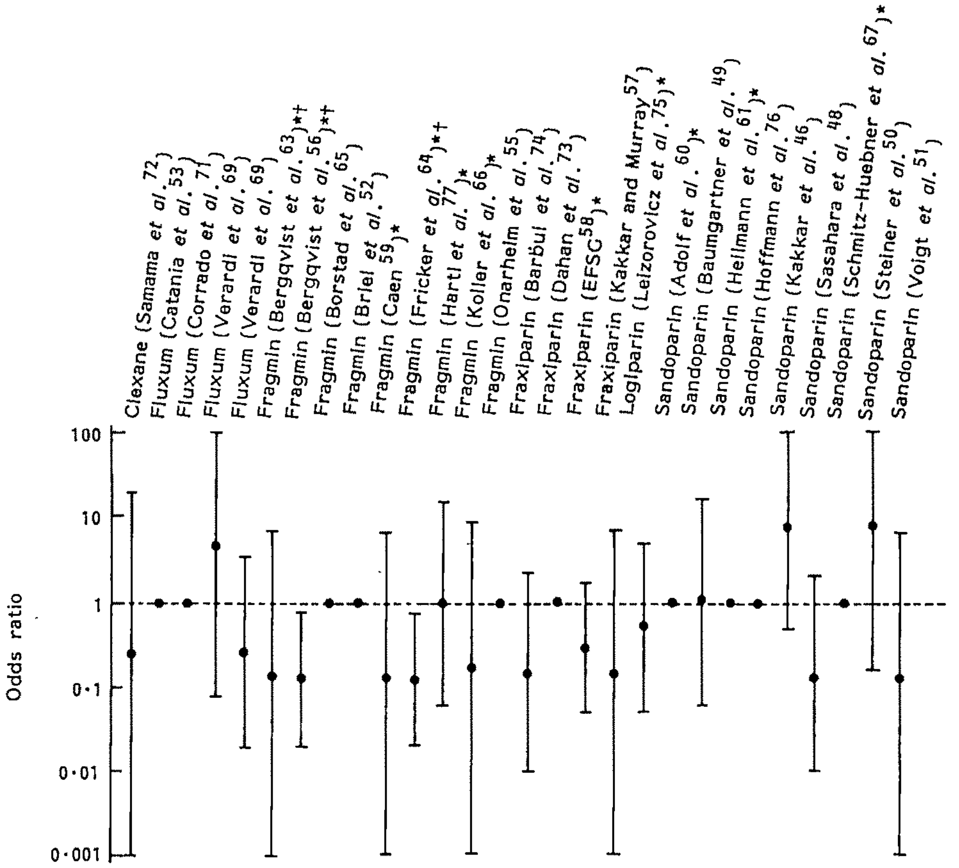

Figure 8 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without dihydroergotamine) on the incidence of pulmonary embolism in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quality studies; † typical odds ratio 0·13 (95 per cent confidence interval 0·04–0·42)* (P < 0·05)

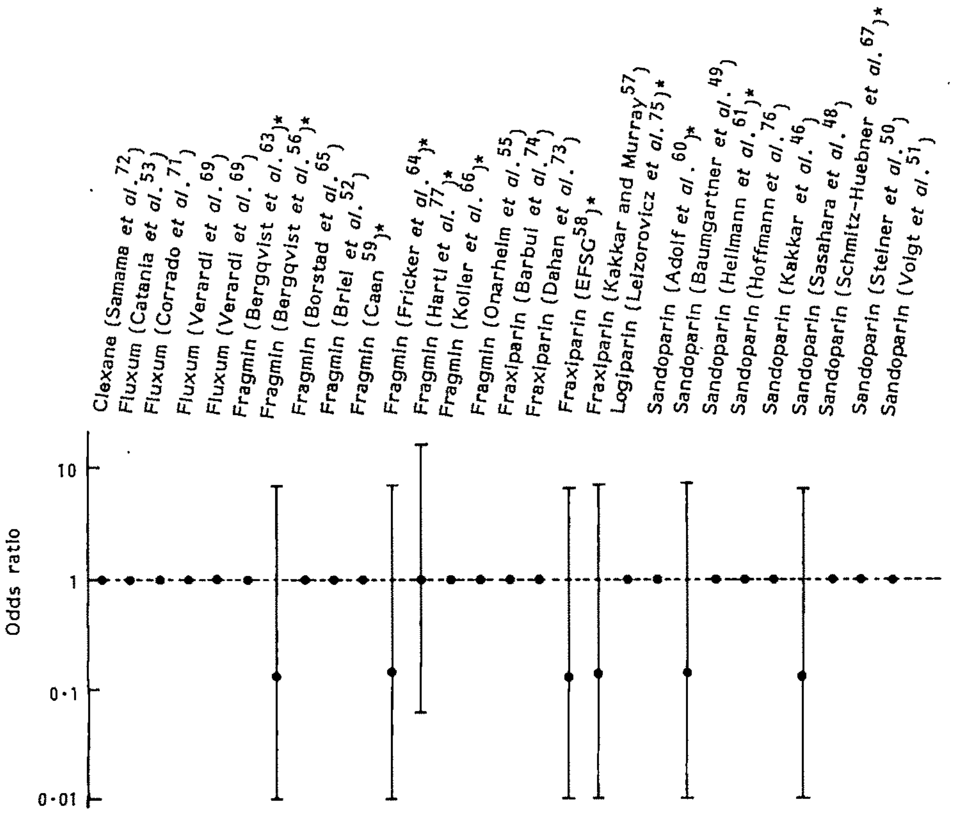

Figure 9 *Effect of low molecular weight heparins (with or without dihydroergotamine)* versus *unfractionated heparin (with or without dihydroergotamine) on the incidence of fatal pulmonary embolism in general and gynaecological surgery. Bars are 95 per cent confidence intervals. * High-quality studies*

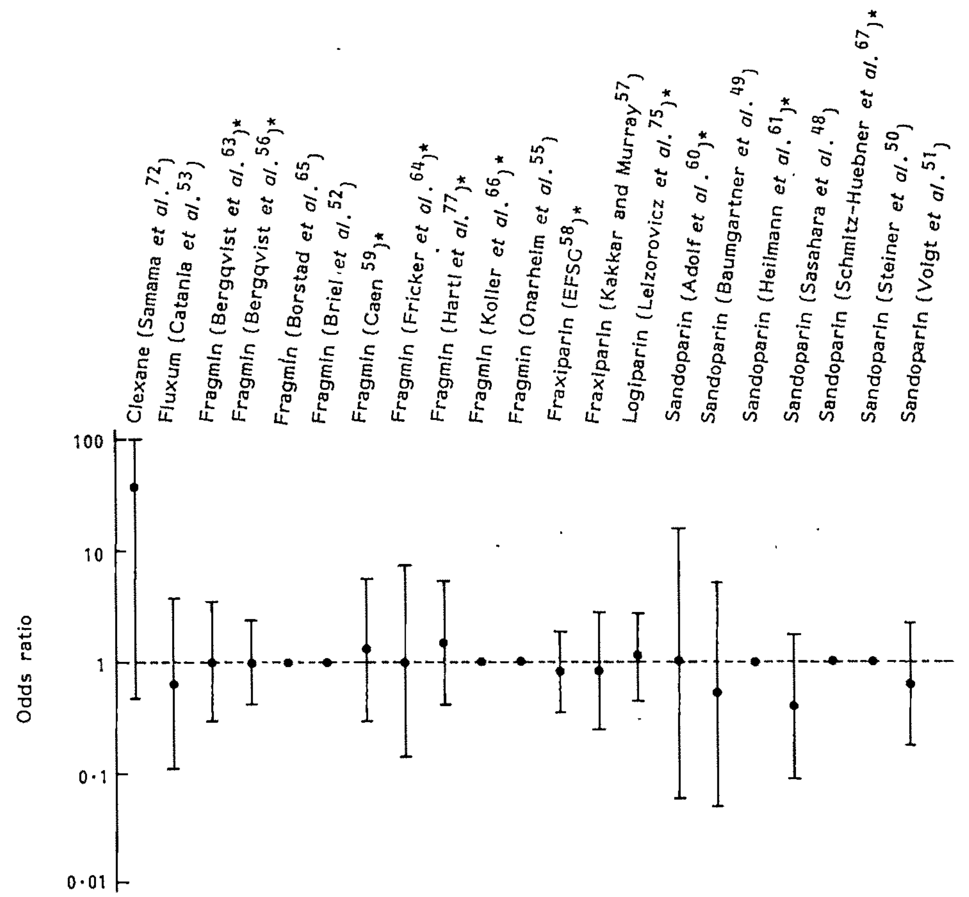

Figure 10 *Effect of low molecular weight heparins (with or without dihydroergotamine) versus unfractionated heparin (with or without dihydroergotamine) on overall mortality rate in general and gynaecological surgery. Bars are 95 per cent confidence intervals. *High-quality studies*

No increase in transfusion requirements of Fragmin-treated patients was observed in any study using this LMWH at 2500 units daily[59,66,77] or in the second trial of Bergqvist *et al.*[56], in which the preoperative 5000-unit Fragmin dose was administered 12 h before surgery. No clear difference in transfusion requirements between the treatment groups was observed in the large studies with Clexane[72], Fraxiparin[58] and Logiparin[75]. The Sandoparin trials are difficult to evaluate because of inconsistent treatment regimens in both unfractionated heparin- and LMWH-treated groups. Most of the studies on Fluxum lack information on transfusion. If the studies are considered as a whole, disregarding the type and dose regimens, there is no indication of a transfusion-saving effect associated with LMWHs.

Discussion

During the past two decades the need to prevent postoperative thromboembolic complications has gained wide acceptance, the final goal being to eradicate the 'silent killer' – fatal pulmonary embolism – which, despite the use of prophylaxis, is still a major concern. Postoperative DVT causes considerable morbidity, with the potential risk of later chronic venous insufficiency. There is no doubt that the use of proper prophylaxis reduces both the postoperative morbidity and mortality rate from thromboembolism. A simple prerequisite is that prophylactic treatment should not be forgotten. Many regimens are not applied in daily practice because of fear of bleeding complications and the burden of such extra therapy to the patient. The development of the LMWHs offers some promising aspects; the drugs are effective on a once-daily basis and do not require paraclinical monitoring. When used in equivalent antithrombotic doses, LMWHs theoretically should, based on animal experiments, cause less bleeding than conventional unfractionated heparin as they cause less inhibition of thrombin[6,7].

In this analysis the main type of surgery and treatment of the control group have been stratified. Instead of performing meta-analysis of inhomogeneous data, which should be avoided[14], graphical presentation of the risk reduction in each trial has been preferred. As the LMWHs show different pharmacodynamic profiles[10], a regular meta-analysis of a set of trials was carried out only when the same type of LMWH in comparable doses was tested against a uniform control group. Only in such a setting do we regard meta-analysis to be statistically valid, contrary to the recent reviews of Nurmohamed *et al.*[78] and Leizorovicz and co-workers[79] in which meta-analyses were performed without differentiation between drugs. The methodology used in the above two reviews differs from that in the present in several other aspects: the definition of high-quality studies[78] was different, some orthopaedic trials[21,36,37,39,40] were not assessed in both reviews, the follow-up period was often restricted to 7–14 days after surgery, results were pooled irrespective of the LMWH dose given[79], heterogeneous groups of bleeding complications (sometimes including postoperative transfusion requirements) were summed, and asymptomatic (screened by the use of scintigraphy in some of the studies) and symptomatic cases of pulmonary embolism were pooled. In addition, not all patients with reported pulmonary embolism had the diagnosis objectively verified, and embolism rate and mortality rate for elective hip surgery and hip fracture repair were assessed in the same analysis. The conclusions from different overviews of the same subject may differ substantially; compared with the two above reviews, the results of the present analysis for calculation of the incidence of pulmonary embolism were more in favour of LMWHs than unfractionated heparin in both orthopaedic and general surgery. A higher incidence of embolism (especially in patients undergoing orthopaedic surgery and receiving LMWH) was found by both Nurmohamed *et al.*[78] and Leizorovicz and associates[79]. We feel that it is justifiable to consider only those cases of symptomatic pulmonary embolism that have been verified by objective measures; this leads to a much lower incidence and provides a more reliable comparison between unfractionated heparin and LMWHs.

In a review by Bergqvist[80], data were compiled without application of meta-analysis methodology, excluding the possibility of a statistical comparison between treatment groups. It was concluded in that paper that LMWHs are at least as effective as unfractionated heparin. In the present review, it is not known whether publication bias from not publishing negative results is present. Having included all abstracts from conferences, it can only be hoped that such bias is minimized.

Duration of diagnostic follow-up is a keystone of study quality; this is especially true for postoperative fatal pulmonary embolism, since most deaths occur >7 days after surgery[81]. Indeed, Bergqvist and Fredin[82] found that patients who suffered fatal pulmonary embolism after hip fracture repair died at a median of 31 days after operation. Recently, Huber and coworkers[83] reported the incidence of postoperative pulmonary embolism to be increased by 30 per cent if all cases occurring within 30 days of hospital discharge were also included. The results of a substantial proportion of the published studies are erroneously based on a short-term follow-up when thromboembolic complications, injection haematoma and bruising are described; only limited, if any, attention is given to the incidence of late pulmonary embolism. This information must be collected directly from the authors but is not always possible to obtain.

Some LMWHs are more efficient than placebo and dextran in the prevention of DVT in both elective and acute hip surgery. It is also clear that LMWHs are at least as efficient as unfractionated heparin in elective orthopaedic operations. Meta-analysis has shown that Clexane significantly reduces the incidence of DVT compared with unfractionated heparin[21,38]. The combination of DHE and unfractionated heparin, two drugs with synergistic action, has been used widely, especially in hip surgery. Although the prophylactic use of this pharmaceutical combination has been reported to be safe[84], DHE has been withdrawn in many countries as a consequence of reported severe arteriospastic side-effects[85]. On the basis of several trials of the prophylactic use of DHE, these side-effects must be considered extremely rare[3,35,46–51], and the use of LMWH with DHE may still appear attractive as a potential alternative, as the daily dose of DHE may be halved. On the other hand, it seems that LMWH without DHE is as effective as unfractionated heparin in combination with DHE[33,34,86].

This paper has reviewed 27 trials in which LMWHs were administered to 2230 patients undergoing orthopaedic surgery. The reported bleeding complications and transfusion requirements give an overall impression that LMWHs are safe in comparison with placebo, dextran or unfractionated heparin with or without DHE. It must be stressed that there is no evidence of fewer bleeding complications in LMWH-treated patients than in those given unfractionated heparin with or without DHE, unlike reports from experimental studies.

Which LMWH has the highest efficacy:side-effect ratio when applied to orthopaedic patients is unknown. Comparisons between compounds will probably never be performed because of the large number of patients needed for such a study. Efficacy and safety must be documented for each LMWH in different surgical situations. It has been claimed for Clexane that there is a close relationship between the antifactor Xa level and the clinical outcome. The optimal antifactor Xa concentration is narrow because levels <0·1 units/ml are related to the development of DVT and those >0·2 units/ml to bleeding complications[87]. Whether LMWHs are more efficient than other regimens in preventing pulmonary embolism in orthopaedic surgery cannot be assessed with current knowledge, although the present review points towards a reductive effect compared with unfractionated heparin with or without DHE. The easy once-daily administration of LMWHs, possibly leading to a higher compliance rate, combined with a probable gain in efficacy against DVT, argues for the use of LMWHs for prophylaxis in orthopaedic surgery. Whether a synergistic prophylactic effect is obtained from the supplementary use of mechanical devices (graded compression stockings or intermittent pneumatic compression) has yet to be shown.

In general surgery the results again show a tendency towards an overall better antithrombotic prophylactic effect using LMWHs compared with unfractionated heparin. So far, LMWHs have not been tested in acute general surgery. It is natural to believe that LMWHs are at least as effective as unfractionated heparin, which is of proven effect, especially when combined with compression stockings[88]. The combination of graded stockings and LMWHs was used in only two studies[58,67]; further evaluation of this combination is lacking. By analogy with the synergistic effect of the combined use of unfractionated heparin and mechanical devices in patients undergoing elective surgery[89], better prophylaxis might be expected by combining LMWHs with compression stockings, but this has so far not been documented.

In some older studies, significantly more bleeding was observed in LMWH-treated patients[63,65–67], but these problems have been solved by altering the dose regimens[56,66,67]. As in the orthopaedic trials, there is no overall indication that LMWHs are associated with fewer bleeding complications than unfractionated heparin, but serious bleeding complications are unusual when recommended doses are employed.

When the high-quality studies in general surgery were analysed, it was found that Fragmin reduced the incidence of symptomatic pulmonary embolism compared with unfractionated heparin. That this could not be shown statistically for the other compounds is probably related to the limited number of investigations rather than to a real difference between the efficacy of different compounds. The incidence of fatal pulmonary embolism was not significantly reduced by any LMWH. To prove a reduction in the number of fatal pulmonary embolisms with LMWHs in general surgery compared with unfractionated heparin, a study of over 50000 patients is needed. To prove a reduction in total perioperative mortality rate, even larger numbers are required. This does not seem feasible, and it must still be remembered that the clinical interpretation of such a study would require a thorough analysis of cost–effectiveness, facing the fact that LMWHs are still more expensive than unfractionated preparations. The biggest apparent advantage of LMWHs in general surgery is their efficacy by once-daily administration.

It has recently been stated that prophylaxis of DVT with LMWH will benefit orthopaedic but not general surgical patients[78,90]. The present review is partly supportive of this; the percentage reduction in the risk of DVT appears comparable in the two groups of patients, but the incidence of such thrombosis is higher in orthopaedic surgery, leading to a greater absolute number of cases of DVT prevented. Thus, use of a LMWH may be more cost effective in orthopaedic surgery despite the higher price of the drug. If future large-scale trials confirm the tendency in the present literature of a reduced incidence of pulmonary embolism through the use of LMWHs in general surgery, the statement above may have to be modified.

The doses in LMWH prophylactic regimens have been widely examined. The present recommendations for orthopaedic surgery are: 3200 units once daily or 2400 units twice daily (Clexane), 5000 units once daily or 2500 units twice daily (Fragmin), 30–50 units/kg once daily (Fraxiparin) and 50 units/kg once daily (Logiparin). For general surgery, the recommended doses are: 1600 units once daily (Clexane), 2500–5000 units once daily (low- and high-risk patients, Framin), 2500 units (equivalent to 7500 Institute Choay Units) once daily (Fraxiparin) and 3500 units once daily (Logiparin). Even though the optimal plasma concentration of antifactor Xa is 0·1–0·2 units/ml, the differences between the drug doses recommended are considerable and may reflect the pharmacological inhomogeneity of the preparations and the variation in present clinical documentation. Much concern has been expressed on the antifactor Xa:antifactor IIa ratio of LMWHs with regard to the bleeding risk and antithrombotic efficacy. Whether this ratio is clinically relevant today is a matter of debate. It has been shown that the plasma antifactor Xa level does not correlate with the incidence of thromboembolism[32] or with that of excessive bleeding in patients undergoing hip surgery[91]. Clinical results have shown that the early findings in animal models of a reduced bleeding tendency with LMWHs, compared with unfractionated heparin in equiantithrombotic doses, should not be extrapolated to humans.

Despite the considerable accumulation of literature on LMWHs, some problems must still be solved. The optimal time for beginning and especially for stopping prophylaxis has to be established. Too few data on the efficacy of combinations with mechanical methods of prophylaxis are available. Although it seems safe to combine lumbar extradural or spinal anaesthesia with a LMWH, a review of reported cases of intraspinal bleeding complications in this situation is particularly needed.

Conclusions

The use of LMWHs for prophylaxis against postoperative thromboembolic complications has not been fully evaluated. In orthopaedic surgery, LMWHs are at least as efficient as other regimens in the prevention of DVT and pulmonary embolism. In general surgery, there may be a better prophylactic efficacy against DVT and pulmonary embolism compared with unfractionated heparin. However, no difference between LMWHs and unfractionated heparin with respect to the number of fatal cases could be detected. With the recommended doses, the routine use of the drugs is safe with respect to bleeding complications and transfusion requirements. A major advantage of LMWHs is that they are efficient when administered once daily; this benefits nursing routines.

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Vibration white finger

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Vibration white finger (VWF) occurs in workers who use vibrating tools. On exposure to vibration or cold, patients experience blanching, numbness and pain in the fingers due to exaggerated vasoconstriction. This may involve both central sympathetic hyper-reactivity and local vasoactive factors. In advanced cases, hypertrophy of vascular smooth muscle causes arterial occlusion and ulceration. Diagnostic tests for VWF are unreliable. In early cases, cessation of vibration exposure arrests the progression of disease and may cause symptom remission. Patients with VWF should keep themselves warm, especially their hands, which they should place in warm water at intervals during the day; they should not smoke. Vasoactive drugs may be beneficial in some patients. In the UK, Industrial Injuries Disablement Benefit and compensation are sometimes available. Improved design of tools and restrictions on their operating time have been the main factors leading to a worldwide decline in the incidence of VWF since the early 1970s.

Vibration white finger (VWF) occurs in workers who have used vibrating tools for many months or, more usually, for years. Tools associated with the development of VWF are pneumatic tools, rotary burring tools, swaging or fettling tools, chain saws, chipping hammers, grinders, concrete vibrothickeners and concrete-levelling vibrotables. In Britain these devices are used mostly in the manufacturing and construction trades[1], and approximately 20000 workers suffer from moderate or severe VWF.

VWF is sometimes called 'Raynaud's phenomenon of occupational origin' because the symptoms of VWF are similar to those of Raynaud's syndrome. In the earliest stages of the condition, vibration induces slight numbness and tingling of the fingers. With continued exposure to vibration, blanching of the fingertips occurs in response to cold, accompanied by numbness of the affected skin. Eventually whole fingers can become involved. In addition to cold, emotion can occasionally induce symptoms. Classically, a triphasic colour change is observed: blanching, then cyanosis and finally rubor. The last feature is due to reactive hyperaemia which terminates the attack and is often accompanied by great pain[2]. Some sufferers do not exhibit any of these colour changes[3]. In advanced cases chronic cyanosis of the affected fingers may develop and approximately 1 per cent of all cases of VWF progress to ulceration or gangrene[4].

Pathogenesis

In 1862 Raynaud suggested that the syndrome that bears his name was caused by hyper-reactivity in the sympathetic nervous system generating episodic vasoconstriction of the digital arteries. Later, in 1929, Lewis suggested that a 'local fault' in blood vessels was to blame. Most modern theories of the pathogenesis of VWF are based on these ideas.

Central sympathetic hyper-reactivity

The evidence for central sympathetic hyper-reactivity in VWF is strong and includes the following:

1. Proximal nerve blockade produced by, for example, application of lignocaine at the finger base eliminates the exaggerated vasoconstrictor response to cold[5].
2. Systolic time intervals are shorter in workers exposed to vibration than in controls[6,7].
3. Urinary excretion of free catecholamines is higher in vibration-exposed groups[6-8].
4. The degree of heart rate variation arising from respiratory arrhythmia correlates with parasympathetic activity; it is reduced in patients with VWF[9-11].
5. Symptoms of autonomic dysfunction are commoner among workers exposed to vibration. These include sweating, headache, vertigo, diarrhoea or constipation, depression, orthostatic hypotension, impotence, fatigue and insomnia. These systemic effects are fully accepted only in Japan and the Commonwealth of Independent States, where they are considered symptoms of 'vibration syndrome'[12-14].
6. There is an immediate improvement in patients with Raynaud's syndrome after thoracodorsal sympathectomy[15].

Central sympathetic hyper-reactivity may arise from prolonged activation of vibration-elicited central sympathetic vasoconstrictor reflexes[16,17]. In addition, vibration-exposed workers are often subject to high levels of cold and noise which cause activity in the sympathetic nervous system[18].

Local vascular changes

Hyper-reactivity of the central sympathetic system cannot be the sole cause of VWF because whole-body cooling alone does not usually provoke Raynaud's phenomenon[19]. Furthermore, the blanching in VWF is well demarcated and distributed in the areas of strongest vibration exposure[20], which suggests that local changes play a part.

The local change could be at the level of the adrenoceptors on vascular smooth muscle. Phenylephrine (which stimulates α_1-adrenoceptors) produces less vasoconstriction in patients than in controls, indicating α_1-adrenoceptor dysfunction[21,22]. On exposure to cold, plasma guanosine 5'-cyclic monophosphate levels rise more in patients with VWF than in controls, indicating a hyper-response of the α_2-adrenergic mechanism[10]. It appears that finger skin circulation in patients may feature functional dominance of α_2- over α_1-adrenoceptors. It has been suggested that only α_2-adrenoceptor-mediated vasoconstrictions are augmented on cooling, so that α_2 dominance in the finger skin circulation may contribute to the cold-induced vasoconstriction seen in VWF[23]. On the other hand, thymoxamine, an adrenoceptor antagonist that displays a 10:1 ratio of α_1:α_2 blocking activity[24], is often effective in

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relieving symptoms of primary Raynaud's disease[25], suggesting that α_2 dominance may not be the cause of this condition.

Hypertrophy of vascular smooth muscle in the arteries and arterioles of symptomatic fingers has been reported[26]. In addition, some patients have a reduced number of finger nailfold capillaries[27], although maximum blood flow following vasodilatation appears to be normal in both early and advanced disease[28,29]. Some studies have found a normal systolic pressure gradient from the upper arm to the most affected finger in patients with VWF; obliterative lesions would cause a steeper gradient[16,30,31]. While some investigators have found obliterative lesions using arteriography[32], others have not[33,34]. These contradictory findings may be reconciled by the observation that vascular obstructive changes are present only in severe cases of VWF[35].

Hypertrophy of vascular smooth muscle may be a late change in the pathogenesis of VWF that exacerbates vasoconstriction elicited by the central sympathetic cold response. In very advanced cases the lumen of the digital arteries narrows substantially; attacks of vasoconstriction cease and are replaced by permanent cyanosis[36]. At this stage, trophic skin changes can occur in the fingertips. Hypertrophy of vascular smooth muscle could be a response to prolonged smooth muscle contraction during episodes of digital vasospasm. In addition, endothelial damage caused directly by vibration may lead to platelet adherence, aggregation and release of mitogenic mediators. One such mediator is platelet-derived growth factor, a mitogenic factor that enters the vessel wall causing focal proliferation of smooth muscle cells. Another is 5-hydroxytryptamine (5-HT), which causes platelet aggregation and vasoconstriction of large vessels; 5-HT also causes vasodilatation of the microcirculation, and the treatment of patients with Raynaud's syndrome with ketanserin, a 5-HT$_2$-receptor antagonist, has variable results[37–43].

Other local mediators that may be important in the pathophysiology of VWF include the eicosanoids. A raised thromboxane B$_2$ level has been found in patients with VWF[44]; this is a metabolite of thromboxane A$_2$, which is a potent vasoconstrictor. The local release of relaxing factors, such as prostacyclin, may fall due to vibration. Serum from patients with Raynaud's syndrome inhibits prostacyclin production[45]. There have been few investigations so far into the role of local mediators in VWF; this might be a fruitful area for further research.

Latency

The latency of VWF is the number of years that elapse from the start of vibration exposure to the development of symptoms. Individuals differ in their sensitivity to vibration. Women, the young and those of asthenic build are the most susceptible[46]. Different types of vibrating tools are associated with different latencies, largely because they cause different kinds of vibration.

In the late 1960s it was found that low-frequency vibration produces the most subjective discomfort. The importance of low frequencies was therefore 'weighted' relative to high frequencies[47,48]. Some physiological evidence supports this weighting; for example, vibration in the range 40–200 Hz reduces cutaneous blood flow substantially, and 120 Hz is especially powerful. All present standards and guidelines are frequency weighted, although it has recently become apparent that high-frequency vibration may be more harmful than was originally believed. Therapists who have been exposed to very high vibration frequencies (around 1 MHz) from the handles of ultrasound devices have impaired vibration perception[49]. Some studies have found a higher incidence of VWF than would be predicted from the guidelines[50], possibly because of high-frequency vibration[51]. Conversely, a study involving tools that emitted a great deal of low-frequency vibration has indicated that the International Organization for Standardization guidelines have overestimated the risk of vibration[52]. A further criticism of the guidelines is that they do not take account of the impulsiveness of vibration. Highly impulsive vibration (that which exhibits a large difference between the peak acceleration and the root mean square acceleration) may be especially dangerous[47].

Prevention

VWF may be prevented by ensuring that vibrating tools are used only intermittently, even if the total operating time is appreciably lengthened[53]. Frequent rests from vibration exposure should be taken during the working day and cyclical job rotation within the workplace should allow some days to be totally free from exposure. If intermittent use is impossible, use of the tool in different positions and at varying angles may be helpful. One of the simplest preventive measures is to instruct workers to hold their tools more loosely[46] because transmission of vibration between tool and hand is proportional to the cubic root of the compression force of the grip[54]. Furthermore, a strong grip force decreases joint elasticity, which also encourages the transmission of vibration[55].

The grip force required to support and control a tool increases with the weight of the device, so heavy tools are more likely to cause VWF. Old chain saws were two to three times heavier than modern devices[55]; they also had 20–30 times larger vibration magnitudes. Longitudinal studies have revealed a fall in the prevalence of VWF since the introduction of antivibration chain saws in the early 1970s[50,56,57]. Although better tool design may help, it should be appreciated that badly maintained equipment may emit high levels of vibration. The fitting of mechanical filters into tool handles and the use of antivibration gloves reduce the operator's ability to manipulate the tool and so such measures are disliked by workers. Although normal gloves provide little protection against vibration and may even amplify it[54,58], they do keep the hands warm, which may be beneficial. Preventing occupational exposure to cold may both inhibit the onset of VWF and help to prevent those who already have the disease from experiencing attacks at work. Tobacco consumption probably hastens the onset and aggravates the symptoms of VWF[59,60].

The UK Health and Safety Executive is introducing a programme aimed at identifying workers at risk in the foundry industry, and in shipbuilding and ship repair yards. A computerized system will measure vibration in workers' hands, allowing those identified as at risk to use the tools for shorter periods, or the tools to be adapted.

Diagnosis

The patient's description of symptoms and the history of vibration exposure are the cornerstones of diagnosis. The number of years of vibration exposure, the types of tool used and (if no objective record is available) the patient's estimation of daily exposure time are all relevant[61]. Alternative causes of secondary Raynaud's phenomenon, such as scleroderma, need to be excluded. Care should be taken to distinguish between the symptoms of primary Raynaud's disease and those of true VWF (*Table 1*).

The patient's description of symptoms and the presence or absence of trophic skin changes allow the condition to be graded on the Stockholm Workshop Scale (*Table 2*). Each hand is staged separately and the number of affected fingers taken into account. Thus '1L(2)/–' indicates Raynaud's syndrome of stage 1 in the left hand affecting two fingers, with a symptom-free right hand. A variety of objective tests is available to confirm a diagnosis of VWF but none has a high predictive value and they are often season dependent, even under controlled conditions[20].

Cold provocation tests

Immersion of the hands to the wrists in water at 10°C for 10 min will provoke an attack in some patients. The colour of the fingers or skin temperature restitution can then be assessed[31,61–65]. Alternatively, only the most severely affected

Table 1 *Differences between the symptoms of primary Raynaud's disease and those of vibration white finger*

Primary Raynaud's disease	Vibration white finger
Pallor tends to be diffuse, sometimes with no clear demarcation from surrounding normal skin	Well demarcated localized blanching
Blanching may occur in toes	Blanching does not occur in toes
Symmetrical	Distribution correlates with the strongest vibration exposure
Most common in women of child-bearing age (15% prevalence); 5% prevalence in men	Occurs in workers exposed to vibration

Table 2 *Stockholm Workshop Scale for the classification of cold-induced Raynaud's phenomenon in the hand–arm vibration syndrome*

Stage	Grade	Description
0		No attacks
1	Mild	Occasional attacks affecting only the tips of one or more fingers
2	Moderate	Occasional attacks affecting distal and middle (rarely also proximal) phalanges of one or more fingers
3	Severe	Frequent attacks affecting all phalanges of most fingers
4	Very severe	As for stage 3, with trophic skin changes in the fingertips

Based on Gemne *et al.*[20]

digit is cooled and the finger systolic blood pressure measured[31,60,61,63].

Other tests

Skin temperature over the back of the middle phalanx of the four fingers may be measured under controlled conditions; <30°C is abnormal and <26°C very abnormal[62]. It has been claimed that spastic, atonic, 8-shaped, twisted nailfold capillaries indicate VWF[46], and a reduction in the number of nailfold capillaries has also been reported[27]. The time taken for a nail to regain its colour after compression may also be used as a test[62]. However, all laboratory tests for VWF are unreliable; any patient who has been exposed to hand–arm vibration daily for many years, and who reports symptoms of VWF for which no other explanation can be found, must be considered to have the disease.

Treatment

Vibration exposure should be terminated. If the disease is mild, this measure alone may cause symptom remission. In advanced cases symptoms will persist and may even deteriorate, especially in patients aged 45 years and over[66]. Abstinence from tobacco is highly recommended[3,59,67] and avoidance of caffeine has also been advised[68]. Ergotamine preparations and β-adrenergic blockers should not be used, because these drugs exacerbate Raynaud's symptoms. Exposure to cold should be avoided and the hands kept warm. A range of heated gloves is available; information about these may be obtained from the Raynaud's and Scleroderma Association*. Placing the hands in warm water for 5 min every 4 h during the day increases resting blood flow[69] and may be beneficial. A minority of patients may need drug therapy. There has been much research into the pharmacological treatment of Raynaud's syndrome, but little of this is specific to VWF.

Sympatholytic drugs

Buflomedil and thymoxamine are α-adrenoceptor blockers with a relatively low incidence of adverse effects that are efficacious in the treatment of Raynaud's syndrome[24,70]. Thymoxamine has been recommended as the first-line drug in primary Raynaud's disease[25]. The effectiveness of buflomedil and thymoxamine in VWF is unknown.

Calcium channel blockers

Nifedipine increases skin blood flow by 50–150 per cent in normal subjects and 30–60 mg daily produces subjective improvement in most patients with Raynaud's syndrome[67,71,72]; 10 mg three times a day, orally, is a recommended initial treatment, rising to 20 mg three times daily if side-effects are absent[3,71,73]. Side-effects of nifedipine therapy are common and include headache, vertigo, peripheral oedema and hot flushes. Some patients experience no benefit from the drug[71,73] and one study found that the efficacy of nifedipine was significantly lower than that of ketanserin[40]. Nicardipine[74] and diltiazem may also be effective agents.

Antagonists of 5-hydroxytryptamine

Ketanserin is a relatively new drug that antagonizes 5-HT$_2$ receptors. However, reports of ketanserin efficacy in Raynaud's syndrome are inconsistent[37–43] and its value in the treatment of patients with VWF has yet to be established. The drug is usually well tolerated, the most common side-effects being dizziness, somnolence and headache, but in very rare cases it may cause severe and sometimes fatal cardiac arrhythmia.

Prostanoids

Iloprost is a prostacyclin analogue that produces vasodilatation and inhibits platelet aggregation. It has been shown to alleviate the symptoms of Raynaud's phenomenon in patients with systemic sclerosis[75,76]. However, prostanoid analogues may have severe side-effects, such as headache, dizziness, vomiting and diarrhoea. Fish oil dietary supplements, rich in the long-chain ω-3 polyunsaturated fatty acids eicosapentaenoic acid and decosaphexaenoic acid, may cause an increased synthesis of prostaglandin I$_3$, which has vasodilatory effects[25]. They have been claimed to improve cold tolerance in primary Raynaud's disease. Evening primrose oil contains eicosapentaenoic acid and is available without prescription.

Angiotensin-converting enzyme inhibitors

Captopril is a potent vasodilator that acts by inhibiting angiotensin-converting enzyme and decreasing the catabolism of kinins. In one study, low-dose treatment with captopril was effective in 50 per cent of patients with Raynaud's syndrome of mild to moderate severity[77].

UK social security and industrial compensation

Social security

In 1985 VWF became a prescribed disease, number A11, and it is now the most commonly reported industrial disease in the UK. Disability is rated on a scale from 0 to 20 per cent and the score may be aggregated with that from another disability. Industrial Injuries Disablement Benefit[78] cannot normally be claimed for disability < 14 per cent. Benefit for disability in the range 14–20 per cent is £18·32 per week (April 1993 to April 1994)[79]. Only 31 of the 5401 patients notified in 1990–1991 received benefit for VWF alone, although some others may have reached the benefit threshold by aggregation of a VWF disability with that from some other prescribed disease (usually occupational deafness). The number of patients with VWF

**Address: Raynaud's and Scleroderma Association, 112 Crewe Road, Alsagar, Cheshire ST7 2JA, UK* claimimg Disablement Benefit has been rising, possibly because of increased awareness among affected groups.

Industrial compensation

In the UK, compensation from employers may be obtained in two ways. The first is common law damages and requires negligence on the part of the employer to be proven. This is an extremely difficult and unpredictable area of litigation that is rarely successful. As a result, in 1986, the General, Municipal and Boilermakers' Union, the Amalgamated Engineering Union and other trades unions agreed a compensation scheme with the main engineering industry insurance company, the Iron Trades Confederation. Awards of up to £2000 are available (J. O'Hara, personal communication).

Vibration disease

In Japan, VWF is considered to form part of a condition that encompasses the whole body: vibration disease. This condition includes symptoms of autonomic dysfunction (such as sweating, headache, orthostatic hypotension, impotence and fatigue), oedematous swelling of the fingers, hearing loss[18,80–82], skeletal changes[83], tendon disorders and muscular stiffness, pain and weakness[84,85]. Loss of pain sensitivity and impaired temperature discrimination are common findings in fingers affected by VWF[62,65,86–88]. These features are caused by peripheral neuropathy which may be diffuse or due to the coexistence of carpal tunnel syndrome. An increased incidence of carpal tunnel syndrome among workers exposed to vibration has been widely reported[83,84,89–91], although whether such individuals benefit from carpal tunnel decompression is questionable[92,93].

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Digest

SURGERY TODAY
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Professor Yoshio Mishima of Surgery Today (The Japanese Journal of Surgery) *has this month selected the best from January to March for his summary. A digest of* BJS *for the same period appears in the Japanese journal.*

Surgical infection

Takesue *et al.*[1] investigated the production of staphylococcal enterotoxin by methicillin-resistant *Staphylococcus aureus* (MRSA) with respect to coagulase type. A total of 138 strains of MRSA isolated from clinical material in the surgical ward between 1983 and 1990 were studied. Coagulase type IV strains produced enterotoxin A only, whereas those of type II were classified into four groups according to enterotoxin production: enterotoxin B-producing strains (32·7 per cent), C-producing strains (29·8 per cent), B- and C-coproducing strains (12·5 per cent), and A- and C-coproducing strains (25·0 per cent). Some 90 per cent of organisms isolated from the faeces of patients with MRSA enteritis were enterotoxin A and C coproducers. The contemporaneous nature of MRSA enteritis and isolation of A- and C-coproducing bacteria demonstrated that these strains caused the enteritis. Although enterotoxin C-producing strains and A and C coproducers were simultaneously prevalent in 1990, the former tended to be sensitive whereas the latter were generally resistant to minocycline. Considering the range of antibiotic sensitivities in coagulase type II bacteria, it is therefore considered very important for epidemiological purposes to characterize isolates further by enterotoxin typing.

Various toxic factors induced by endotoxin are thought to be involved in the pathogenesis of severe infection. Ono *et al.*[2] examined the role of platelet-activating factor (PAF) in these conditions, clinical and experimental studies being conducted on the relationship between PAF and changes in general parameters after surgical infection. In a clinical study, changes in PAF concentration in the blood of seven patients with disseminated intravascular coagulation (DIC), five with sepsis and two without, were monitored by spectrometry. The mean PAF level in patients with DIC and sepsis was higher than that in those without sepsis. Moreover, in the former the increase in PAF level with time was found to show a negative correlation with the platelet count. Experimentally, the role of PAF in toxic shock and the effect of an anti-PAF agent and protease inhibitor were investigated. The endotoxin-induced fall in blood pressure was prevented by both the anti-PAF agent and the protease inhibitor. The decrease in platelet count was more significantly inhibited by the anti-PAF agent than by the protease inhibitor but the blood coagulation–fibrinolysis system was more affected by the protease inhibitor.

Oesophageal varices

The results of 44 terminal oesophagoproximal gastrectomies and 53 oesophageal transections for varices, performed between January 1975 and March 1989, were reviewed retrospectively by Shiozaki *et al.*[3]. The results examined prognosis, recurrence of varices and late postoperative complications. The 5-year survival rates for patients undergoing selective or prophylactic surgery were 85·9 per cent following oesophagoproximal gastrectomy and 81·6 per cent after oesophageal transection. The 10-year survival rate after the former procedure was significantly lower than that after the latter (59·3 *versus* 70·0 per cent, $P < 0{\cdot}05$) because of the number of deaths from haemorrhage caused by anastomotic ulceration and from liver failure. The respective 5-year rates for recurrence of varices after oesophagoproximal gastrectomy and transection were 18·4 and 26·4 per cent, respectively, while the 10-year recurrence rate for the former procedure was again significantly lower than that for the latter (27·1 *versus* 53·7 per cent, $P < 0{\cdot}01$). Reflux oesophagitis and/or anastomotic ulcer were found twice as frequently after oesophagoproximal gastrectomy as after oesophageal transection. Although proximal gastrectomy was more effective for preventing variceal recurrence it left the potential for anastomotic ulcer to develop, which was the dominant cause of death for up to 5 years after surgery.

Stomach

Kaibara *et al.*[4] examined 1606 patients with gastric carcinoma to ascertain whether the frequency of primary tumours in organs other than the stomach was higher in patients with multiple gastric cancers than in those with a single gastric tumour. Cancers of other organs were present in 87 (5·9 per cent) of 1474 patients with a single gastric cancer and in 16 (12·1 per cent) of 132 with multiple gastric tumours. This difference was statistically significant. The most frequent site of a second tumour was the colorectum, followed by the urogenital organs, uterus, breast and lung in descending order of frequency. The occurrence of multiple cancers in the stomach is not merely a chance phenomenon but may be related to genetic predisposition and environmental factors.

Rectum

Konn *et al.*[5] compared morbidity, survival and recurrence rates in 203 patients treated by curative low anterior resection with those in 100 undergoing curative abdominoperineal resection (APR). The overall 5-year survival rate(s.e.) was 75·6(5·7) per cent: 79·8(6·4) per cent for low anterior resection and 67·7(9·6) per cent for APR. The prognosis for patients with tumours situated low enough in the rectum to involve the anal canal was poor even when managed by APR, as evidenced by a low survival rate(s.e.) at 5 years of 59·0(9·6) per cent and a high pelvic recurrence rate of 34·0 per cent. Low anterior resection proved at least as good as APR as a curative method for middle and low rectal cancers, on the basis of the 5-year survival rate(s.e.) being 79·8(6·4) *versus* 78·7(5·2) per cent, the operative mortality rate being 1·5 *versus* 1·0 per cent, the morbidity rate 39·4 *versus* 59·0 per cent, and the incidence of pelvic recurrence 8·9 *versus* 13·5 per cent. Low anterior resection should, therefore, be attempted for every lesion except those that are very advanced or have anal canal involvement.

Endocrine surgery

According to Kasuga *et al.*[6], of 847 consecutive patients with Graves' disease who underwent thyroidectomy between 1965 and 1990, 4·3 per cent were found to have coincident carcinoma of the thyroid. In 68 per cent of these patients the tumours were <1 cm in diameter and were detected in only seven (19 per cent) before surgery. Dissection of the regional lymph nodes was necessary in only 11 patients. A review of the patients in 1990 revealed no deaths related to carcinoma, with metastases occurring most commonly in patients with larger tumours and in those in whom cancer had been detected before thyroidectomy. Although the preoperative detection of

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potential tumours occurring with Graves' disease using ultrasonography may be of interest, the results suggest that occult microcarcinoma coincident with this condition is not clinically significant as it is rarely associated with recurrence. There was no evidence to suggest that Graves' disease was associated with an increased or rapid growth of thyroid tumours.

Total parathyroidectomy with autotransplantation has been widely accepted as the appropriate treatment for patients with hyperparathyroidism after chronic renal failure on long-term haemodialysis. The treatment of recurrent disease has been problematic. Tanaka *et al.*[7] studied 128 patients followed for >2 years after surgical treatment. Preoperative serum parathyroid hormone (PTH) concentrations correlated with the total weight of the parathyroid glands. When the original autotransplanted glands were divided into two groups (diffuse and nodular), the rate of recurrent hyperparathyroidism from graft hyperfunction was significantly higher in patients who received nodular than in those who received diffuse glands (24 *versus* 8 per cent, $P < 0{\cdot}05$). To investigate whether PTH synthetic activity is different in diffuse and nodular glands, the amount of PTH messenger RNA was studied by *in situ* hybridization. There was no significant difference in the amount of PTH message in cells from diffuse and nodular glands. These data suggest that the recurrence of hyperparathyroidism results not from enhanced PTH synthetic activity of autotransplanted grafts but from the abnormal growth rate of the transplanted gland.

Endoscopic surgery

Palmar hyperhidrosis is a troublesome and embarrassing disorder that causes occupational, psychological and social problems. Its aetiology is unknown, although surgical therapy by thoracic sympathectomy is probably the treatment of choice. Numerous methods of sympathectomy, including open thoracotomy as well as posterior and supraclavicular approaches, have been described. Chou *et al.*[8] favour endoscopy because of its simplicity and short hospital stay. Between March 1988 and October 1990, 112 patients (55 male, 57 female; age range 15–45 years) suffering from palmar hyperhidrosis underwent 222 thoracoscopic T2–T3 sympathectomies under general anaesthesia. The remaining two sides required a second operation by unilateral thoracotomy because of pleural adhesion. A total of 220 hands became dry and the others showed improvement. Five patients required unilateral chest tube insertion: two for drainage after thoracotomy and three for intrathoracic haemorrhage after thoracoscopic pneumolysis. The mean operating time (bilateral) was 30·8 min and mean hospital stay 2·9 days. The major complication was compensatory hyperhidrosis. There was no death. Thoracoscopic sympathectomy is a simple, safe and effective method of treating palmar hyperhidrosis.

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Digest

The American Journal of Surgery®

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For this quarter's digest Dr Hiram Polk has selected from the January to March issues of The American Journal of Surgery. *A summary of the best of the* BJS *written by Professor John Farndon appears in the June issue of the American journal.*

Surgical training

Progressive differentiation, euphemistically termed superspecialization, is occurring among US physicians, and surgery is not immune to this change. Intrinsic to this process is what will be left of the basic discipline of surgery. John Cameron's presidential address to the Society for Surgery of the Alimentary Tract provides a new level of discussion and some data supporting the value of fellowships in mainstream alimentary tract surgery after residency[1].

Of all the proposals for further differentiation, none strikes so close to the heart of surgery itself. Professor Cameron argues that such a fellowship will increase the prestige and attractiveness of gastrointestinal surgery. An example might be the complex operations on the pancreas, permitting greater depth of experience for fewer trainees. These issues have been addressed in some major cancer centres where there is no competition between 'chief residents in surgery' and 'surgical oncology fellows'. Accomplishing this without prejudicing the fundamental education of the trainee general surgeon is difficult. Historically, Dr Cameron's institution has been at the forefront of surgical education but the current climate in North American surgery and medicine will make such change more difficult now than ever before.

Gastric cancer

For some time, the only good news about gastric cancer was its declining prevalence in North America. Sindelar and his group[2] at the National Cancer Institute evaluated intraoperative radiotherapy as a novel treatment and, although expense and inconvenience were not examined, the trial demonstrated measurable efficacy. There was no survival advantage but control of local disease was improved: seven of 16 patients treated suffered locoregional recurrence compared with 23 of 25 controls ($P < 0\cdot001$).

Gastrinoma

Stabile and colleagues[3] emphasized the importance of gastrinoma location from the perspectives of localization and overall clinical behaviour. The latest report demonstrates that gastrin-secreting tumours to the right of the superior mesenteric artery (SMA) are more common; 36 per cent were extrapancreatic, 20 per cent multiple and 64 per cent metastasized to lymph nodes. Only 20 per cent of patients had hepatic metastases and 43 per cent were cured. In contrast, tumours to the left of the SMA were multiple in 44 per cent of cases and all were intrapancreatic. Some 56 per cent had liver metastases and only one of 16 patients was cured. This very different behaviour suggests that these tumours may have different aetiologies.

Oesophageal varices

Rikkers and associates[4] describe a randomized prospective study of shunting *versus* sclerotherapy for patients with bleeding varices and cirrhosis. Sixty patients were randomized between 1982 and 1988 and followed for a mean of 87 months. Patients receiving shunts fared better with respect to overall survival and rebleeding. This is an uncommon trial that will seldom, if ever, be repeated in the USA; economic issues will drive patients towards preferred sclerotherapy and few surgeons will develop and retain the expertise to provide selective shunt operations. The report defines the long-term value and cost-effectiveness of portasystemic shunting, especially for selective or distal splenorenal shunts, in a precise fashion.

Hepatobiliary surgery

Deziel and colleagues[5] from Chicago report a national survey from many hospitals of more than 77000 laparoscopic cholecystectomies. These data are important to the surgical practitioner to provide statistical and scientific validity to rare events, such as retained stones and bile duct injuries. How do these numbers relate to conventional biliary tract surgery and the data existing before the introduction of laparoscopic surgery 4 years ago? It would seem that the *ad hoc* learning experience that initially characterized this operation in the United States has largely come to an end and that most residents are now trained in the standard format typical of traditional surgical procedures for the past 100 years. It may be that the 'learning curve' issues that may have been influential in this survey are no longer applicable and that patients will have benefited accordingly.

Regional and geographical variations in surgery present fascinating problems. Hepatolithiasis is a common phenomenon in the Far East, and Fan and colleagues[6] at the Queen Mary Hospital in Hong Kong have described the use of hepaticocutaneous jejunostomy in the lifelong management of this condition. They suggest that such a procedure can be helpful in the temporary and longer-term management of selected patients with complicated forms of proximal biliary and hepatic disease.

Antibiotics

There may be some value to refine further the issue of the dose and method of administration of commonly used antibiotics to optimize surgical value. Leading proponents of this school have been Livingston and Wang[7], who have shown that large doses of antibiotics may reverse some of the 'immunosuppression' associated with shock and resuscitation. The authors now raise the issue of a continuous infusion of a standard antibiotic being more valuable than its intermittent administration. Much still needs to be learned in this field.

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Breast

Mammography has become a political issue in the United States; recent studies suggest that it may not be of value in younger women. This notwithstanding, it has been the most widely accepted diagnostic tool for cancer in American medicine in the past 20 years and the practising surgeon is overwhelmed with large numbers of women with non-palpable mammographic abnormalities that justify biopsy. Grannan and Lamping[8] show that local anaesthesia as a method of approaching this is as good as general anaesthesia. The implications in a cost-conscious society for a common procedure are obvious.

The continued refinement of prognostic factors in breast cancer seems to be both politically and scientifically correct. Aaltomaa and colleagues[9] at Kuopio University Hospital in Finland studied a large number of women followed for >8 years with a detailed analysis of prognostic factors. Certain growth patterns indicated by mitotic indices and nuclear morphometric variables were of limited value in determining the prognosis for patients with hormone receptor-negative tumours. The authors suggest that this kind of information is not needed and that cost can thus be contained in an effective way. The detailed results of this study largely reinforce observations that are well known. The quality of the follow-up and its duration are especially helpful, as is this refinement of care for the patient with hormone receptor-negative breast cancer.

Melanoma

The incidence of melanoma is increasing in North America and, despite the latitude dependency of this cancer, a group in Calgary at the Tom Baker Cancer Center makes a new contribution. All doctors who care for patients with melanoma are concerned about the patient with a very thin lesion who develops metastases. Pontikes *et al.*[10] found that the likelihood of recurrence is increased by location in the head and neck or a relatively thick Clark level compared with simple thickness measurements. Changes in thickness *per se* within this group, up to 1 mm, did not have an influence.

The results suggest that identifying such a group with a 10 per cent chance of recurrence will in turn allow selection of patients (the thicker levels in the head and neck) in whom adjunctive treatment is justified. The best adjunctive treatment is not yet determined.

Innovations

Molecular biology has made a number of contributions to medical science, some of which are working their way through to the bedside. A clear example of this is recombinant tissue plasminogen activator (tPA). Evans and associates[11] describe a dose-dependent retardation of adhesion formation associated with the use of tPA, but one which may be correlated with a reduction in wound hydroxyproline content. They conclude that the levels required to alter or prevent intra-abdominal adhesions may represent a significant risk to the early phase of wound repair and the compound needs to be used with care.

Technical innovations in surgery are always appreciated, all the more so when they may provide resolution of a formidable surgical complication. Jorgensen and Hunt[12] from Sydney, Australia, report a method for the endoscopic drainage of oesophageal suture-line leaks that remain contained.

Burns

Care of the patient with burns continues to be a major challenge worldwide. Hypothermia is, of course, common after operative care of patients with major burns. A group in Osaka found that promptness of recovery from postoperative hypothermia is extremely important in predicting outcome and may be helpful both as a specific guide to therapy and in the longer term identification of a high-risk group of patients[13]. Although the number of patients studied was small, the observations are important and the group has used precise techniques to come to these conclusions. The authors suggest that patients who cannot generate heat as needed in conditions of postoperative hypothermia may also be unable to produce the additional energy demand associated with the prevention of later burn wound sepsis.

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Hepatitis B immunization and exposure to blood among surgical staff

A questionnaire was sent to all 158 staff of the operating department of a London teaching hospital to confirm their hepatitis B immunization status and establish the number of incidents involving exposure to blood during the preceding 4 weeks. Of these personnel, 104 (66 per cent) were known to be immune to hepatitis B either through immunization (97) or previous infection (seven). A further 23 (15 per cent) had completed a course of immunization but their seroconversion had not been checked. There were 26 sharps injuries sustained by 14 (12 per cent) of 119 staff and 240 other exposures to blood. Four of the sharps injuries had been reported. Staff known to be immune were more likely than those with unknown or negative immunity to report incidents (20 versus *0 per cent (95 per cent confidence interval of difference 2–38 per cent)). Doctors sustained more non-sharps exposures to blood than others (47* versus *23 per cent (95 per cent confidence interval of difference 7–40 per cent)). An important minority of operating department staff remains unimmunized against hepatitis B, although exposure to blood is common. Incidents are rarely reported and staff with unknown or negative immunity seem less likely to report than those known to be immune.*

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Immunization of operating department staff against hepatitis B not only protects them, but also protects patients against the risk of transmission from an infected worker. Participation in an immunization programme allows the identification of non-responders, a few of whom will be carriers of hepatitis B. Transmission of the virus from infected workers to patients is well recognized[1]. New guidelines from the Department of Health are likely to make immunization against hepatitis B a condition of employment for healthcare workers who perform invasive surgical procedures, as well as precluding those with e antigen from undertaking such procedures.

There is an active hepatitis B immunization programme at the Royal Free Hospital. Immunization clinics are held regularly with provision for staff to attend at convenient times; individuals who default on a course are contacted and managers asked to allow staff time to attend for immunization. Increased awareness has been achieved by writing to consultants, poster campaigns and a 'hepatitis B week' to encourage non-immunized staff to come forward.

A survey of hepatitis B immunization status among staff of the operating department, their experience of incidents involving exposure to blood, and the reporting of such events is described.

Methods

The study group comprised all 158 staff working in the operating department. This included 72 surgeons, 19 anaesthetists, 50 nurses, 11 operating department assistants and six administrative staff. The hepatitis B immunization status of all staff was obtained from their occupational health records and divided into six categories (*Table 1*). Where there was no documentation of immunization in the records, staff were classed as 'unimmunized'. A questionnaire was sent to all 158 personnel with details of their immunization status, asking them to amend the information if it was incorrect. Where relevant they were asked to give reasons why they had not started or completed a course of immunization. Other questions asked staff to estimate how many incidents involving exposure to blood they had sustained in the preceding month and how many of these they had reported to the occupational health unit. Exposures to blood were divided into sharps injuries (for example from needles, scalpels or bone fragments) and other exposures (such as eye and mouth splashes). There were two mailings of the questionnaire, followed by an attempt to contact non-responders by telephone to obtain replies.

To allow comparison of staff known to be immune to hepatitis B with those of unknown or negative immune status, the immunization categories in *Table 1* were combined. Staff classed as known to be immune included those with natural immunity (category 1) together with those in category 6 who had completed a course of immunization and been shown to respond. An assumption was made that those in category 6 who had been immunized and tested elsewhere had also responded, although no evidence of their antibody level was available. Staff of unknown or negative immune status included the remaining categories in *Table 1* and three known non-responders to immunization from category 6.

The proportion of staff suffering one or more incidents involving exposure to blood was calculated and differences compared for occupational group and hepatitis B immune status. The actual number of incidents per subject was further compared on a log scale for these two variables and their interdependence examined using bivariate regression.

Results

A total of 128 staff (81 per cent) responded to the questionnaire: 103 (65 per cent) returned it by post and a further 25 (16 per cent) were questioned by telephone. Of these, 61 doctors (77 per cent) and 45 others (92 per cent) agreed with the immunization status obtained from occupational health records. Many of those who amended their immunization status were doctors who had not participated in the hepatitis B immunization programme run by the occupational health service in the hospital; no information on their immunization status was available in the occupational health records and they had been classified by default as unimmunized, although they had actually been immunized elsewhere.

The number of doctors and non-doctors in each immunization category is shown in *Table 1*. None of the seven staff with natural immunity was a carrier of hepatitis B infection. Sixteen of the 21 staff who failed to start or complete the course of three injections gave reasons, including: difficulty finding time to attend (seven); 'Just haven't got round to it' (five); 'Don't consider myself at risk' (three); not enough information

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Table 1 *Immunization status according to occupation*

Category no.	Status	Doctors	Non-doctors	Both
1	Natural immunity	2 (2)	5 (7)	7 (4)
2	Never started an immunization course	8 (9)	7 (10)	15 (9)
3	Started an immunization course and defaulted	3 (3)	3 (4)	6 (4)
4	Receiving course and awaiting further immunization or antibody test after immunization	6 (7)	1 (1)	7 (4)
5	Completed course but defaulted on immunization antibody test after immunization	16 (18)	7 (10)	23 (15)
6	Completed course and antibody test*	56 (62)	44 (66)	100 (63)
	Total	91 (100)	67 (100)	158 (100)

Values in parentheses are percentages. *Records of protective levels of antibodies after immunization were available for 85 members of staff; three people were known to have failed seroconversion following immunization. The remaining 12 people (eight doctors) had been immunized and tested for response elsewhere; no record of the test results was available

Table 2 *Sharps and non-sharps exposure to blood according to occupational group and hepatitis B immune status*

	Sharps exposure to blood		Non-sharps exposure to blood	
	Proportion with incidents (%)	Log [mean no. of incidents]	Proportion with incidents (%)	Log [mean no. of incidents]
Doctors ($n = 71$)	14	0·146	47	0·825
Non-doctors ($n = 48$)	8	0·058	23	0·299
Difference (95% confidence interval)	6 (−6 to 17)	0·088 (−0·037 to 0·21)	24 (7–40)	0·526 (0·21–0·84)
Known immunity ($n = 87$)	14	0·123	38	0·654
Unknown immunity ($n = 32$)	6	0·078	34	0·501
Difference (95% confidence interval)	8 (−4 to 19)	0·045 (−0·094 to 0·18)	4 (−16 to 23)	0·153 (−0·21 to 0·52)

about risk of infection (two); and not enough information about immunization (one).

In all, 119 respondents gave information about incidents involving exposure to blood during the preceding 4 weeks. A total of 26 sharps injuries were sustained by 14 staff (12 per cent). Four of these injuries were reported to the occupational health service, giving a reporting rate for sharps injuries of 15 per cent. A further 240 non-sharps exposures to blood were sustained by 44 individuals (37 per cent); none of these events was reported. Of the 20 sharps injuries sustained by persons known to be immune, four (20 per cent) were reported, compared with none of the six sharps injuries sustained by those of unknown or negative immunity (95 per cent confidence interval of difference 2–38 per cent). There was no significant association between occupational group and reporting behaviour.

The percentage of staff having one or more incidents of exposure to blood and the mean number of incidents per person are given in *Table 2*. A significantly higher proportion of doctors than non-doctors experienced one or more non-sharps exposures to blood. In addition, the mean number of non-sharps exposures per person was significantly higher among doctors. No significant differences were found between staff classed as known to be immune and those of unknown or negative immunity. Bivariate analysis showed that job category and immune status had independent effects on the mean number of incidents and the proportion having one or more incidents (sharps and non-sharps exposures).

Discussion

This survey shows that 66 per cent of the operating theatre staff have antibodies to hepatitis B either through immunization (61 per cent) or previous infection (4 per cent). Immunization rates of 49, 73 and 87 per cent have been reported[2–4]. These figures are not directly comparable with the present results as some are derived from postal questionnaires with low response rates and one relates to a population reporting needlestick injuries. Moreover, although 87 per cent of Wessex surgeons had been immunized, fewer than half of these had been tested for an antibody response[4]. The true number of staff protected against hepatitis B in the present study could be as high as 127 (80 per cent), as up to 98 per cent of the immunized group who defaulted on the antibody test will have responded to the vaccine[5]. Measurement of an individual's antibody response to immunization is important for several reasons: after a blood contamination incident, a worker who has been successfully immunized can be reassured that he or she is protected against hepatitis B; non-responders can be offered booster injections and if they still fail to respond can be alerted to the importance of reporting contamination incidents early so that passive immunization can be considered; and previously infected individuals who may need further investigation and advice can be identified.

The occupational health records used in this survey were on the whole reliable, with all errors underestimating hepatitis B immunization. This was principally the result of a failure to record details for some doctors immunized elsewhere and the method of obtaining this information from new doctors is now being reviewed.

About 10 per cent failed to start an immunization course; the most common reason given was lack of time. Operating department staff are involved in high-risk activities and should be given the opportunity to attend for immunization. Three respondents said they did not consider themselves to be at risk: two are no longer involved in surgical procedures and one is a consultant surgeon. Of concern is that senior surgeons who do not perceive a risk of hepatitis B infection in surgical practice may communicate this belief to junior members of their surgical team. It is also possible that fear of the consequences of being found to be hepatitis B antigen positive could deter some individuals from participating in an immunization programme.

Doctors were significantly more likely than others to experience non-sharps exposure to blood. This probably reflects the surgeon's proximity to the operating field and hence greater risk of skin contamination. Other staff share with surgeons the risk of sharps injuries, for example when instruments are being passed or cleared away.

There was a low reporting rate of 15 per cent for sharps injuries. Other workers have also commented on low reporting rates for such injuries, especially among doctors[6–8]. The present low rate occurred despite efforts to encourage reporting by talks, leaflets, posters and the provision of a special telephone reporting system. However, the number of reported incidents in this hospital has risen from 146 during 1989 to 229 during 1991. Although knowledge of immunity was not associated with the incidence of exposure to blood (*Table 2*), staff who knew themselves to be immune were significantly more likely than others to report sharps injuries. It may be that those careful enough to have a course of hepatitis B immunization and a subsequent blood test are also mindful of the need to report incidents and to obtain proper advice and management. The proportion of successfully immunized individuals among those reporting incidents could be an overestimate of this group within the whole population at risk. However, there is little difference between the proportion immunized in the present study and that found in the authors' previous review of staff reporting exposure to blood[9]. Imminent new guidelines from the Department of Health are likely to make hepatitis B immunization a condition of employment for workers involved in invasive surgical procedures. Occupational health departments need to address this issue urgently and encourage surgical staff to participate in immunization programmes.

Acknowledgements

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Femoroaxillary bypass for cerebral ischaemia caused by occlusion of the innominate artery

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Extra-anatomic bypass between the axillary and femoral arteries was first described[1,2] in 1963 and in 1971 Sproul[3] used reversed axillofemoral reconstruction to treat stenosis of the innominate artery. Axillofemoral bypass is used as an alternative to aortofemoral reconstruction in patients with lower-limb ischaemia for whom intra-abdominal grafting presents an unacceptable risk. Indications are absolute when there is aortic sepsis, or relative because of technical factors or medical problems. The improved patency rate provided by externally supported polytetrafluoroethylene (PTFE)[4] led to the suggestion that the technique is a viable alternative to aortofemoral reconstruction in patients with uncomplicated occlusive disease. This paper is the first to report femoroaxillary reconstruction using externally supported PTFE for the relief of cerebral ischaemia caused by occlusion of the innominate artery.

Case report

A 76-year-old woman had a 1-month history of episodic dizziness on standing that was worse with sudden head movement. There were no focal neurological symptoms but the attacks were accompanied by visual blurring in the right eye. The woman also suffered from chronic obstructive airway disease and cor pulmonale. The right brachial pressure was 80/60 mmHg but in the left arm it was too low for assessment. The right carotid pulse was absent but over the left carotid artery there was a thrill and bruit. Arteriography showed a 3-cm occlusion of the innominate artery with collateral filling of the right common carotid, right subclavian and right vertebral arteries. At the left common carotid origin was a tight stenosis. The left subclavian artery origin was occluded but slowly filled distally from the vertebral system.

A right femoroaxillary artery graft using 8-mm externally supported PTFE was uneventfully completed. The patient has been symptom-free during follow-up for 2 years and, despite her age, has resumed work. Blood pressure has remained 130/90 mmHg on the right and 110/90 mmHg on the left. Arteriography confirmed satisfactory patency (*Figure 1*).

Discussion

Despite occlusion or major stenosis affecting the vessels supplying the carotid and subclavian territories of one side, a patent ipsilateral or contralateral artery may usually be found for local bypass. Techniques of axilloaxillary, carotidocarotid, axillocarotid and subclavian–carotid reconstruction are well described, and carotid–biaxillary bypass has recently been reported for the treatment of bilateral arm ischaemia[5]. Reconstruction when all aortic branches are compromised requires intrathoracic surgery, which is hazardous in patients with respiratory insufficiency.

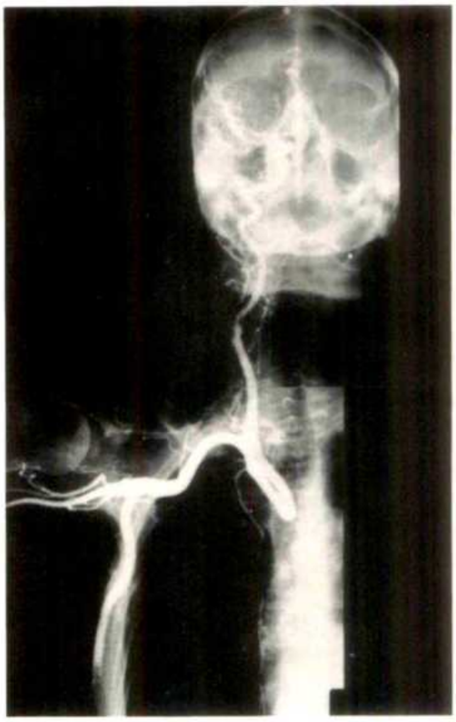

Figure 1 *Arteriogram 18 months after operation showing outflow of the femoroaxillary graft*

Revascularization of the axillary, subclavian and cerebral vessels using a bypass from the femoral vessels is rarely performed, although it has been described in the treatment of the ischaemic upper limb. There is only one report in the literature of femoroaxillary reconstruction to treat stenosis of the innominate artery causing cerebral ischaemia; a 10-mm unsupported knitted Dacron (Du Pont, Stevenage, UK) graft was used[3]. Poor primary and secondary patency rates in axillounifemoral grafts have been improved by recent technical refinements, including the use of externally supported PTFE, which now permits a primary patency rate comparable to that of aortofemoral reconstruction[4]. Most failures during the first year are the result of technical problems or poor outflow.

This first report of the use of externally supported PTFE for femoroaxillary bypass for occlusion of the innominate artery suggests that the procedure is effective and carries a low risk. It is a suitable operation for cerebral ischaemia when there is no adequate inflow vessel in the neck or upper limb to allow a more local bypass.

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Natural history of abdominal aortic aneurysm detected by screening

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A group of 88 patients with abdominal aortic dilatation found in four ultrasonographic screening studies was followed prospectively by repeated ultrasonography. The initial aortic diameter ranged between 18 and 70 mm. In 19 patients (22 per cent) the aortic diameter exceeded 39 mm. The mean(s.e.m.) annual expansion rate of dilatations <40 mm in diameter was 0·8(1·2) mm; among those $\geqslant 40$ mm it was 3·3(1·2) mm. The expansion rate increased with increasing initial diameter. Thirty-eight patients died; the overall mortality rate in the group was high in comparison with an age- and sex-matched population. One patient died after elective aneurysm surgery but none died from a ruptured aneurysm. In conclusion, in about 80 per cent of dilatations found in screening studies the aortic diameter was <40 mm, with a low risk of rupture. One annual rescanning of an aneurysm <35 mm in diameter is sufficient; a high overall mortality rate must be expected.

Screening programmes for abdominal aortic aneurysm (AAA) have sometimes been recommended as a method of decreasing the mortality rate from rupture[1–4]. In a number of studies, ultrasonography has been used for screening[5] and, as a result, aortic dilatation too small to justify elective operation was found. The size of the affected group and the question of how to handle patients with small AAA are not known. Before general recommendations on screening can be made it is important to know the natural behaviour of the disease in the asymptomatic state. For patients with AAA, this means both expansion rate of the aneurysm and likelihood of survival of the patient. Recently, some work has been performed on the expansion rate of the small aneurysm[6–9]. However, no study on AAA detected purely by screening has been reported.

The aim of the present study was to analyse the survival rate and expansion rate of the aorta in individuals found to have aortic dilatation in four ultrasonographic screening studies.

Patients and methods

Between 1986 and 1988 four ultrasonographic screening studies of abdominal aortic dilatation were performed at this hospital. The groups studied consisted of 154 patients[10] (100 men, 54 women) previously treated by carotid endarterectomy, 183 patients[11] (147 men, 36 women) presenting with intermittent claudication between 1970 and 1979, 45 individuals[12] (17 men, 28 women) who were siblings of patients operated on for AAA in Malmö, and a random sample of 364 men, aged 74 years, from Malmö[13]. Four individuals belonged to two groups, one of whom had an aortic dilatation of 35 mm.

Screening was performed by radiologists with a special interest in ultrasonography. Real-time equipment was used. The abdominal aorta was examined along its entire length. Abdominal aortic dilatation was defined as a dilatation distal to the renal arteries or an infrarenal aortic diameter perpendicular to the aortic axis >29 mm. The largest diameter, either anteroposterior or transverse, was used. In the study of 74-year-old men, 35 mm was taken as the upper limit of normality. Patients with aortic dilatation were treated individually with decisions whether and when to operate on the aneurysm or to follow the patient by repeated ultrasonography being made by members of the vascular surgical staff.

The expansion rate of an AAA was calculated as the difference between the first and last measurements of maximum abdominal aortic diameter with respect to time. Patients with aortic dilatation were followed from the date of the first examination to 31 October 1991 or until death if earlier. Death certificates and autopsy protocols were reviewed to establish the cause of mortality.

Results

Aortic dilatation was found in 80 men and eight women. The median age for the men was 73 (range 54–84) years and for the women 74 (range 63–84) years. The median abdominal aortic diameter was 31 (range 21–70) mm among men and 30 (range 18–42) mm among women. Seven dilatations (8 per cent) were $\geqslant 50$ mm and 19 (22 per cent) $\geqslant 40$ mm. *Figure 1* shows a histogram of initial aortic diameter. Of the 88 patients, 41 had stenotic vascular disease and 47 did not; age had no effect as both groups had a mean age of 71 years.

Two or more measurements of aortic diameter were performed in 78 patients (72 men, six women). Six patients died before a second examination, three were operated on after the first investigation and one (aortic diameter 33 mm) refused further examination. The median interval from the first to last measurement was 2·7 (range 0·4–6·4) years. The median change in aortic diameter per year was 0·8 (range −10·0 to 13·4) mm; *Figure 2* shows a histogram of expansion rates. *Figure 3* illustrates the size of individual aortic dilatations and their change in diameter with time. The expansion rate correlated significantly with initial diameter ($r = 0{\cdot}21$, $P = 0{\cdot}03$). The mean(s.e.m.) annual expansion rate of aortic dilatations $\geqslant 50$ mm ($n = 14$) was 6·0(0·4) mm and the median 3·6 (range 3·3–13·4) mm. For dilatations of 40–49 mm ($n = 11$) the

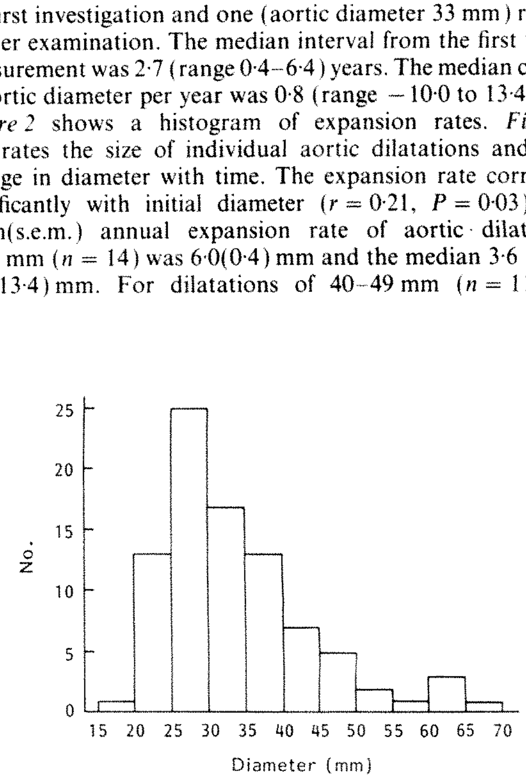

Figure 1 *Maximum abdominal aortic diameter in 88 patients with aortic dilatation detected by screening*

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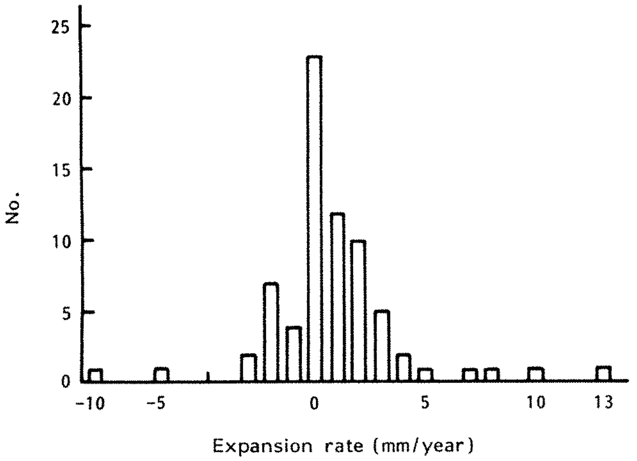

Figure 2 *Expansion rate of abdominal aortic dilatation in 78 patients, measured using ultrasonography*

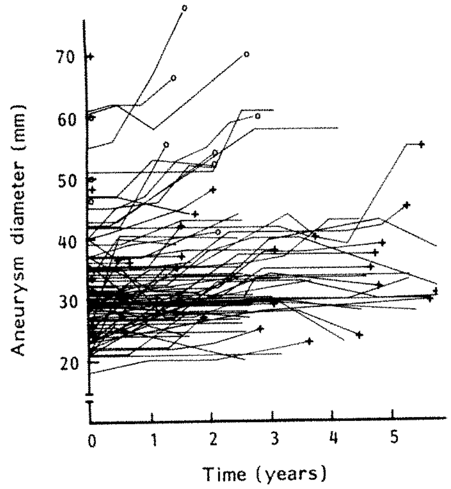

Figure 3 *Individual expansion curves for 88 abdominal aortic dilatations detected by screening.* ○, *Patient underwent elective surgery;* +, *non-aneurysmal death*

mean(s.e.m.) was 2·3(1·4) mm and the median 2·4 (range −7·2 to 10·1) mm. For dilatations $<$40 mm ($n = 63$) the mean(s.e.m.) was 0·8(1·2) mm and the median 0·3 (range −10·0 to 8·2) mm. Dilatations $\geqslant$40 mm in diameter ($n = 15$) expanded by a mean(s.e.m.) of 3·3(1·2) mm and a median of 3·4 (range −7·2 to 13·4) mm annually.

The decision to treat the aneurysm surgically was made by individual vascular surgeons on the basis of clinical judgement. Elective operation was performed on 12 patients; one died after surgery. No emergency operations were carried out. In one patient graft replacement of the aorta was performed because of aortoiliac occlusive symptoms; the last measurement of aortic diameter in this patient was 31 mm. In another the last ultrasonographic measurement of diameter was 41 mm; 6 months later a diameter of 47 mm was measured by computed tomography and the patient underwent operation. One 74-year-old patient was operated on when screening revealed an aneurysm of 48 mm diameter. The remaining nine patients all had an aneurysm $\geqslant$50 mm measured by ultrasonography.

During follow-up, 38 patients (32 men, six women) died. Post-mortem examination was performed in 16 (42 per cent); no patient died from ruptured AAA. The main cause of death was cardiac insufficiency or myocardial infarction in 21 patients, other atherosclerotic disease in six, infectious disease in five and malignancy in six. Patients who died did not differ in age or initial aortic diameter from those alive at the end of follow-up, but 28 had stenotic vascular disease. The cumulative survival rate for patients with aortic dilatation is shown in *Figure 4*, together with that for an age- and sex-matched population in Malmö obtained from the Population Register Bureau[14]. The 2-, 5- and 7-year survival rates(s.e.) for patients with AAA were 84·1(3·9), 60·6(6·0) and 36·2(8·0) per cent respectively. The 95 per cent confidence intervals were below the survival rate for the age- and sex-matched normal population at 5 and 7 years.

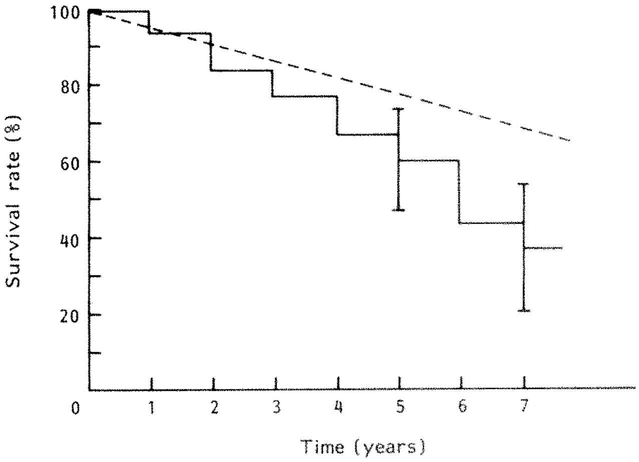

Figure 4 *Survival curves for 88 patients with abdominal aortic dilatation detected by screening (——) and an age- and sex-matched normal population (- - -). Bars are 95 per cent confidence intervals*

Discussion

The decision whether or not to operate on an AAA is often based on the size of the dilatation. An aneurysm of diameter $<$40 mm is considered very unlikely to rupture, whereas one $\geqslant$40 mm has a significant risk[8,15–20]. The pooled results from the present four screening studies suggest that the proportion of aneurysms of diameter $\geqslant$40 mm is 22 per cent. In two other ultrasonographic screening studies of general populations[2,21] the proportions with AAA $>$40 mm were 20 and 31 per cent. This implies that, from screening studies of AAA, probably about 80 per cent of the dilatations found will be too small to justify immediate surgery.

The apparent tendency of some aneurysms to decrease in diameter at least temporarily probably results from observer variability in making ultrasonographic measurements. The reproducibility of such measurements of the abdominal aorta has been studied[22,23] and the discrepancy between different observers found to be 5–7 mm at most. In observations within short intervals this may suggest rapid change in aortic diameter, but over longer time periods and with repeated investigation the effect of variability in measurement is neutralized.

The expansion rate of the present aortic dilatations rose with increasing initial diameter, in agreement with other studies that have included small aneurysms[6,8,16,17]. The relationship between aneurysm size and expansion rate is better described by an exponential than a linear model[19], as was also observed by Limet *et al.*[8]. This means that the expansion rate accelerates with increasing aneurysm size. Aortic dilatations $<$40 mm expand at a median annual rate of 0·8 mm but have a large individual variation (from −10·0 to 8·2 mm per year). If patients observed over a very short period ($<$6 months) are excluded to neutralize the effect of observer variation, the annual expansion rate still varied from −3·8 to 5·8 mm. For practical purposes this suggests that aortic dilatations $<$35 mm need be rescanned only annually to assess when they reach 40 mm.

The mortality rate in the present study was high compared with that of an age- and sex-matched normal population. No ruptured AAA was found in the study group, but one patient died from elective surgery for aneurysm. The majority (71 per cent) died from cardiovascular disease and there was no overt relationship between aneurysm size and death. The higher mortality rate may be explained in two ways. First, patients were recruited from a population that has an increased mortality rate because of generalized atherosclerosis (intermittent claudication and carotid artery disease)[24,25]. Second, patients with aortic dilatation may have an increased incidence of coronary artery disease[26].

In conclusion, it has been shown that about 80 per cent of dilatations found in ultrasonographic screening investigations of populations at potential risk are <40 mm in diameter. The expansion rate of aortic dilatation increases with increasing initial size and dilatations <40 mm, despite large individual variation, very rarely expand >6 mm per year. The mortality rate among patients with aortic dilatation detected by screening is high, not because of AAA rupture but because of frequent advanced atherosclerosis; this should be considered when elective surgery for aneurysm is discussed.

Acknowledgements

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Rupture of a true profunda femoris artery aneurysm

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Peripheral artery aneurysms are uncommon and almost always occur in the lower limb. The popliteal artery accounts for 55 per cent and the common femoral artery for 42 per cent of aneurysms of the leg[1]. Aneurysms of the profunda femoris artery (PFA) are estimated to represent 0·5 per cent of all peripheral artery aneurysms but are rarely considered as a cause of thigh swelling and are often missed, with subsequent limb loss. A ruptured PFA aneurysm in which the diagnosis had been missed, with potentially catastrophic consequences, is reported.

Case report

A 77-year-old man suddenly developed a painful swelling in the left thigh while on holiday abroad. He continued his 2-week vacation and on return to the UK was referred by his general practitioner to hospital where an 8-cm abdominal aortic aneurysm was found on ultrasonography. The patient was concerned that he was scheduled for abdominal operation only to repair the aortic aneurysm and requested a second opinion. The man had had no previous cardiac or cerebrovascular disease and no symptoms of intermittent claudication. He was anaemic, with left upper thigh swelling and bruising over the medial aspect. Bilateral femoral and popliteal artery aneurysms were identified with all peripheral pulses palpable. Routine laboratory investigations revealed a hypochromic microcytic anaemia (haemoglobin level 8·8 g/dl; all other indices were normal). Colour Doppler ultrasonography demonstrated a large aneurysm arising from a connection with the left PFA. Computed tomography of the pelvis and upper thighs confirmed aneurysms of the abdominal aorta and both common iliac arteries. In the upper thigh there was a 10-cm diameter heterogeneous soft tissue mass continuous with the profunda femoris vessel with a clear soft tissue plane between it and the superficial femoral artery on all sections (*Figure 1*). This aneurysm was confirmed by arteriography (*Figure 2*).

Laparotomy revealed a 7-cm aneurysm of the aorta and right common iliac artery, with a 3-cm aneurysm of the left internal iliac artery. A massive aneurysm in the left thigh contained 2 litres of old thrombus and blood clot, and communicated freely with a ruptured aneurysm of the left PFA 8 cm from its origin. After cross-clamping, the aortic and iliac aneurysms were opened and the lumbar arteries under-run with polyglactin sutures. The left external and internal iliac arteries and right external iliac arteries were oversewn with polypropylene, and an 8-mm Dacron (Du Pont, Stevenage, UK) tube graft sutured into the origin of the right internal iliac artery. A 22 × 11 mm bifurcation graft was anastomosed end to end to the infrarenal aorta. Both limbs were directed retroperitoneally and anastomosed end to end to the common femoral bifurcation, and the right internal iliac graft was sutured end to side to the right limb of the bifurcation graft. The aneurysm in the left thigh was opened and the feeding PFA ligated proximally and sutured distally. After surgery the patient developed a lymphocele of the right groin wound which required aspiration daily. This collection became infected and 24 days after surgery ruptured the right limb of the graft. The infected limb of the graft was replaced with a rifampicin-coated straight graft as an emergency. At 4 months after surgery the man remains well, with normally perfused legs.

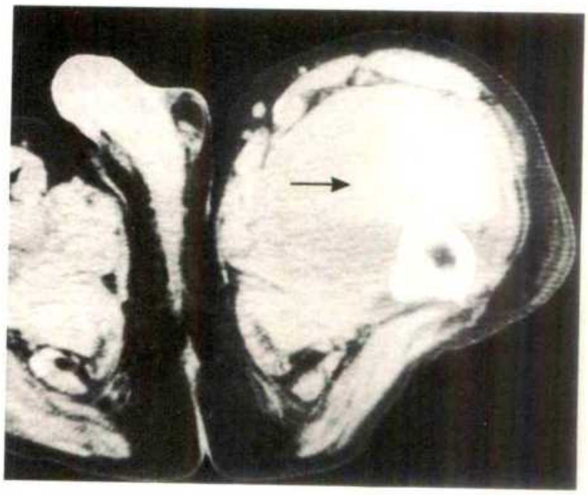

Figure 1 *Computed tomogram showing contained rupture (arrow) of the profunda femoris artery aneurysm*

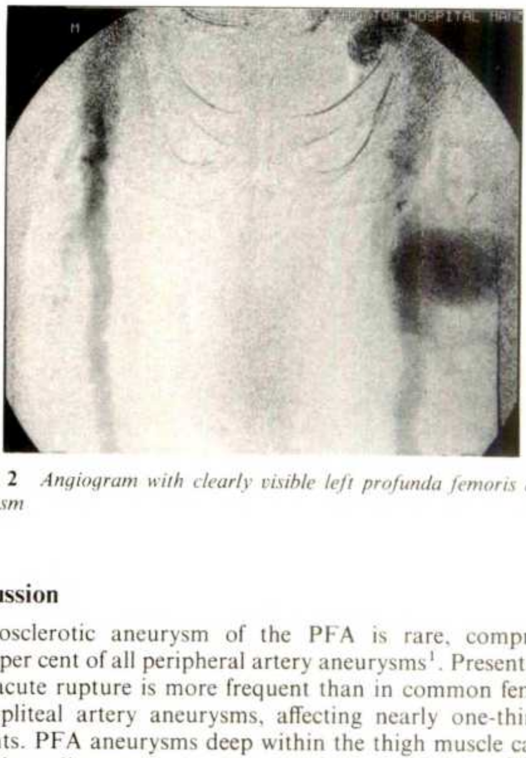

Figure 2 *Angiogram with clearly visible left profunda femoris artery aneurysm*

Discussion

Atherosclerotic aneurysm of the PFA is rare, comprising $<0·5$ per cent of all peripheral artery aneurysms[1]. Presentation with acute rupture is more frequent than in common femoral or popliteal artery aneurysms, affecting nearly one-third of patients. PFA aneurysms deep within the thigh muscle can be difficult to diagnose and many may remain undetected[2].

False aneurysm of the profunda femoris and common femoral arteries may arise following trauma or complicating diagnostic procedures and orthopaedic operations on the upper femur and hip[3,4]. True aneurysms are rare, the relative immunity of the PFA to their formation having been ascribed to its passage through the muscle bulk of the medial thigh[5].

Rupture of a PFA aneurysm is rare. If the superficial femoral artery is patent, it may be treated by ligation with or without reconstructive bypass surgery. Elective repair of an aortic aneurysm ignoring the profunda rupture would almost certainly have led to limb loss. This patient still has bilateral popliteal artery aneurysms.

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Short note

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Benefits of carotid endarterectomy: the message is not getting through

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Two large international trials have shown that carotid endarterectomy is better than medical therapy alone in the long-term prevention of ischaemic stroke in symptomatic patients with severe ($\geq$70 per cent) carotid stenosis, whereas medical therapy is indicated in those with minor (<30 per cent) stenosis[1,2]. At 8 months after the initial publicity surrounding these important studies, a postal survey was conducted among 454 general practitioners in Leicestershire to see whether the trials had influenced attitudes towards referral and investigation.

Results

In all, 276 general practitioners (61 per cent) responded to the questionnaire; only 57 of these (21 per cent) were aware of the results of the European and North American trials. Of these 57, only 26 (46 per cent) had increased their referral practice, 29 (51 per cent) noted no change and two (4 per cent) had actually decreased their rate of referral as a consequence.

Overall, 112 practitioners (41 per cent) stated that they would usually or always refer patients for investigation after their first cerebral ischaemic event (transient ischaemic attack, amaurosis fugax or minor stroke), while 159 (58 per cent) would usually or always administer aspirin and take no further action. Of the latter group, however, 99 (62 per cent) would then refer the patient if they suffered a second ischaemic event. General practitioners were more likely to refer patients who were <70 years of age (90 per cent) or had a carotid bruit (91 per cent). The largest single group (42 per cent) referred patients to vascular surgeons; 91 (33 per cent) sent patients to a general physician and 44 (16 per cent) to a neurologist for investigation.

Discussion

Although this study is representative only of the 276 general practitioners in Leicestershire who responded, it does suggest that the results from the two international randomized trials have not adequately reached the body of doctors who are involved with the first-line care of patients with cerebrovascular disease. Moreover, even if the unlikely assumption is made that the 39 per cent of non-responders were all aware of the trial results, the fact remains that 50 per cent of general practitioners in Leicestershire were not. This may be because both articles were, not unnaturally, published in mainstream hospital journals. However, there was considerable national press interest at the time. Even when the 40 per cent or so who usually refer their patients for investigation after a single cerebral ischaemic event are excluded, the majority (60 per cent) will still usually administer aspirin and take no further action until, or unless, the patient presents either with a second ischaemic episode or has a carotid bruit. That the majority of general practitioners place so much emphasis on the presence of a carotid bruit is worrying, as this may be absent in those with the most severe carotid stenosis[3], i.e. the very group that has the most to benefit from endarterectomy.

The two trials[1,2] have cost a huge amount of money and considerable effort on the behalf of the many collaborating centres. While we still await guidance on the relative roles of surgery and medical therapy in the management of symptomatic patients with moderate carotid stenosis (30–70 per cent), it is clear that greater effort must be expended in transmitting the positive results achieved thus far to those who provide our primary healthcare service. For our part, we propose to circulate to general practitioner colleagues the results of this questionnaire and hope to provide a more accessible outpatient and duplex ultrasonography service to enable rapid and appropriate planning of investigation and management in the future.

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Use of desmopressin to prevent bleeding complications in patients treated with aspirin

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Aspirin induces a haemorrhagic diathesis that persists for at least 1 week after discontinuation of the drug. The effect of the vasopressin analogue desmopressin was studied in 12 patients treated with aspirin who were undergoing cholecystectomy. Desmopressin was given to six of these patients. There were five postoperative bleeding complications; all occurred in patients who had not received desmopressin ($P < 0{\cdot}05$)*. The bleeding time was prolonged in aspirin-treated patients and normalized by desmopressin* ($P < 0{\cdot}05$)*. Desmopressin can be used safely to prevent bleeding induced by aspirin.*

Aspirin is one of the most widely used drugs in the world and is increasingly employed in the prevention of cardiovascular disease. Other non-steroidal anti-inflammatory drugs with principally the same mode of action are widely used as analgesics. The effect of these drugs in the inhibition of platelet function[1] is of increasing concern.

Desmopressin ([1-deamino-8-D-arginine]vasopressin) is a synthetic analogue of vasopressin without vasopressor activity. It induces the release of coagulation factor VIII, von Willebrand factor and tissue plasminogen activator from the endothelium. It is used to achieve appropriate haemostasis in patients with mild forms of haemophilia A and von Willebrand's disease who undergo surgery. Moreover, desmopressin is effective in uraemia, liver cirrhosis and several other conditions associated with defects of platelet function[2].

The aim of this study was to investigate the effect of desmopressin on aspirin-induced prolongation of bleeding time and blood loss in patients undergoing surgery.

Table 1 *Details of 18 patients* undergoing cholecystectomy*

	Aspirin (*n*=6)	Aspirin plus desmopressin (*n*=6)	Control (*n*=6)
Sex ratio (M:F)	2:4	2:4	1:5
Mean(s.d.) age (years)	55(9)	48(11)	51(8)
Mean(s.d.) operation time (min)	120(76)	91(47)	83(37)
Mean(s.d.) intraoperative blood loss (ml/h)	159(94)	86(87)	86(83)
Postoperative bleeding episodes	5†	0‡	0
Blood transfused (units)	4	0	0
Mean(s.d.) preoperative bleeding time (min)		7·4(1·2)†	5·0(2·2)
After desmopressin		5·5(0·8)§	
Mean(s.d.) postoperative bleeding time (min)		5·9(0·7)	5·0(1·1)
After desmopressin		3·9(0·7)§	

*Twelve patients received aspirin for 5 days before surgery and six of these were given desmopressin before and after operation. †$P < 0{\cdot}05$ (*versus* control, Mann–Whitney *U* test); ‡$P < 0{\cdot}05$ (*versus* aspirin alone, Mann–Whitney *U* test); §$P < 0{\cdot}05$ (*versus* before desmopressin, Wilcoxon signed rank test)

Patients and methods

Patients

Eighteen patients undergoing elective cholecystectomy were studied (*Table 1*). They were all non-obese, without a history of bleeding episodes or thrombotic events, and with normal liver function, serum lipid and blood glucose levels. Informed consent was obtained from each patient before operation. The protocols were approved by the committee of ethics at Karolinska Institute. The administration of desmopressin was approved by the National Swedish Board of Health.

Drug administration

Six patients received aspirin (Dispril; Meda, Göteborg, Sweden), 500 mg twice daily for 5 days, taking the last dose on the evening before surgery. Six patients were given desmopressin (Minirin; Ferring, Malmö, Sweden) and aspirin as above. Desmopressin (0·3 μg per kg body-weight) was given twice – just before the induction of anaesthesia and 6 h later – and was infused intravenously over 20–30 min. Six patients were included as untreated controls and received neither aspirin nor desmopressin.

Anaesthetic and surgical procedure

Anaesthesia was induced with fast-acting barbiturate and maintained with fentanyl, nitrous oxide and enflurane during muscle relaxation and endotracheal intubation. Cholecystectomy was performed via a right subcostal incision. Intercostal blockade with bupivacaine and intramuscular injection of ketobemidone was used for postoperative pain relief. Pharmacological prophylaxis of thrombosis was not used.

Bleeding parameters

The bleeding time was determined according to a modification of Ivy's method, with the Surgicutt device (Ortho Diagnostic Systems, Edison, New Jersey, USA) and 40 mmHg stasis (normal range 1·8–7·0 min). This was carried out before and after both doses of desmopressin. In control patients the determination was made before surgery and 6 h later. Intraoperative blood loss was recorded. After operation a bleeding episode was recorded when the wound dressings had to be renewed because of bleeding. Circulatory instability with a significant fall in haemoglobin level for no apparent reason was also considered to indicate a postoperative bleeding episode.

Statistical analysis

Comparisons were carried out using the two-tailed Mann–Whitney *U* test and the Wilcoxon signed rank test[3].

Results

The mean preoperative bleeding time in patients receiving aspirin was prolonged to 7·4 min, compared with a mean in control patients of 5·0 min ($P < 0{\cdot}05$) (*Table 1; Figure 1*). Each dose of desmopressin significantly reduced the bleeding time ($P < 0{\cdot}05$), which remained within the normal range after the first desmopressin infusion.

There were five postoperative bleeding episodes, all in patients receiving aspirin alone (*Table 1*). Four patients had bleeding from the wound requiring a change of dressing and the fifth episode was noted when a patient experienced vertigo and had a haemoglobin level of 8·3 g/dl on the third day after operation (preoperative level 13·9 g/dl, intraoperative blood loss 250 ml). In the control and desmopressin plus aspirin

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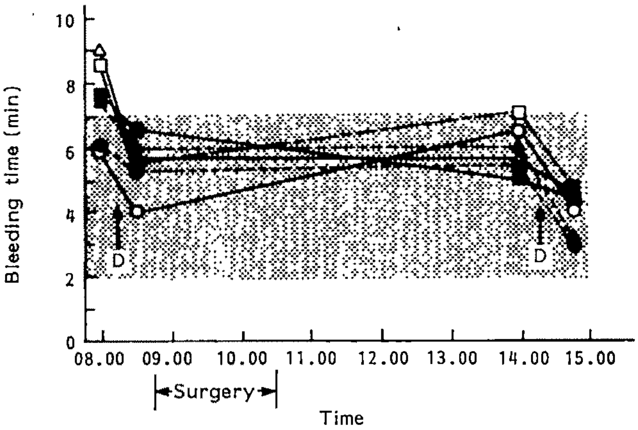

Figure 1 *Bleeding times in six patients undergoing cholecystectomy who were treated with aspirin plus desmopressin.* ▨, *Normal range; D, desmopressin infusion*

groups there were no postoperative bleeding episodes. The difference was statistically significant ($P < 0\cdot05$).

All patients had facial flushing without discomfort for 15–30 min after the first desmopressin dose, but none after the second. No other side-effects attributable to desmopressin were noted.

Discussion

Aspirin-treated patients undergoing cholecystectomy had a haemorrhagic diathesis, as shown by a prolonged bleeding time and high incidence of bleeding episodes after surgery. Desmopressin prevented bleeding complications and normalized the bleeding time in such patients. This is in accordance with previous studies, which have shown that desmopressin normalizes the prolongation of bleeding time induced by aspirin in volunteers[4,5] and aspirin-treated patients not undergoing surgery[6,7]. The use of desmopressin to achieve normal surgical haemostasis after aspirin ingestion has previously been reported in a single case[6]; this, however, is the first report of a series.

Aspirin irreversibly inhibits the transformation by cyclo-oxygenase[1] of arachidonic acid into prostacyclin and thromboxane A_2. Prostacyclin, synthesized mainly in the vascular endothelium, is an inhibitor of platelet adhesion. In the presence of higher levels of aspirin, prostacyclin synthesis is depressed; at lower levels, synthesis recovers. Thromboxane A_2, formed mainly in platelets, promotes platelet adhesion. The synthesis of thromboxane A_2 cannot recover after aspirin administration because of the irreversible inactivation of cyclo-oxygenase; mature platelets have no nuclei and cannot, therefore, synthesize protein[1]. Thus, aspirin inhibits platelet function because it inactivates synthesis of proaggregatory thromboxane A_2 for the rest of the life of the platelet (about 10 days on average), but leaves the production of antiadhesive prostacyclin largely unaffected.

Thromboxane synthesis does not recover after desmopressin administration. The mechanism of its effect in aspirin-induced platelet dysfunction involves the release of larger than normal von Willebrand multimers, which are particularly effective in binding platelets to subendothelial collagen[2].

The bleeding time determination made after the first desmopressin dose may have underestimated the effect of the drug. It was carried out immediately after a 20-min infusion, but the peak of the von Willebrand factor increase is not achieved until 1–2 h after infusion[2]. Moreover, the rapid infusion of the first dose caused obvious temporary dermal vasodilatation in all patients, and the blood flow during that bleeding time determination was about fivefold greater than during all others. This increased blood flow may have flushed away platelet aggregates, making the bleeding time inaccurately prolonged.

No adverse effects were noted, apart from short-lasting facial flushing after the first dose. There are reports of patients in whom coronary artery thrombosis was suspected, and it has been recommended that desmopressin be used cautiously in those with atherosclerosis[8]. However, the number of reported cases has been only 1 per 50 000 patients treated[9]. In a review of all studies of patients undergoing cardiopulmonary bypass surgery, there was the same incidence of thrombotic events in desmopressin- and placebo-treated patients[9]. There is no evidence of an increased risk of venous thrombosis[10] or of disturbances of water–electrolyte balance in patients undergoing surgery[11].

It is concluded that desmopressin normalizes aspirin-prolonged bleeding time in patients undergoing surgery. This is the first study to show a simple and uncomplicated way of preventing the surgical bleeding complications induced by a non-steroidal anti-inflammatory drug.

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Patterns of venous reflux in limbs with skin changes associated with chronic venous insufficiency

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The distribution of venous reflux in patients with skin changes associated with chronic venous insufficiency presenting to a specialist clinic was assessed. A total of 300 limbs in 153 patients were examined by Doppler ultrasonography with colour-flow imaging for the presence of venous reflux in superficial veins, deep veins and medial perforating veins, both above and below the knee. Ninety-eight limbs had skin changes, which included hyperpigmentation, lipodermatosclerosis, atrophie blanche and ulceration. Of this group, 2 per cent had no evidence of venous reflux on duplex scanning, 39 per cent had deep vein incompetence, 57 per cent had superficial vein incompetence and 2 per cent had isolated medial perforating vein reflux. Of 25 limbs with ulceration, 13 had superficial and 12 deep vein reflux. A total of 202 legs, which included 20 normal control limbs, had no skin changes; 22·3 per cent of these had no venous reflux, 8·4 per cent had deep vein incompetence, 65·3 per cent had superficial incompetence and 4·0 per cent had isolated medial calf perforating vein incompetence.

Skin changes associated with chronic venous insufficiency, including lipodermatosclerosis, atrophie blanche and ulceration, may be associated with incompetence of superficial veins[1], deep veins[2] and calf perforating veins[3]. The reported relative incidence of incompetence at each of these sites varies, with several different diagnostic techniques being used. Some venographic studies[4–6] have demonstrated a high incidence of post-thrombotic changes in these limbs, suggesting that deep vein incompetence is a common cause of skin changes; 40 per cent of patients with venous ulcers have objective evidence of post-thrombotic damage[7].

Venography, however, has disadvantages in the diagnosis and assessment of deep venous disease in that it is invasive, often uncomfortable for the patient, and has an associated morbidity[8], although this is less since the introduction of non-ionic contrast media. For these reasons, venography cannot be repeated frequently. The non-invasive technique of duplex scanning overcomes many of the problems associated with venography. It has been used for the diagnosis of acute deep vein thrombosis[9] and, more recently, in that of venous incompetence of the lower limb[10]. This study classifies limbs with and without skin changes of chronic venous insufficiency according to the site of venous incompetence on the basis of duplex scanning with colour-flow imaging.

Patients and methods

A total of 300 lower limbs in 153 patients from a venous outpatient clinic, which included those referred by general practitioners and from other physicians and surgeons within the region, were investigated.

Limbs were examined with an Acuson 128 scanner (Acuson, Mountain View, California, USA) with colour-flow imaging facility using a 5-MHz pulsed Doppler probe. Scanning was performed with the patient standing on a low platform to fill the veins and to allow reflux to occur following contraction and relaxation of the calf muscle as a result of the effect of gravity. Cephalad venous flow was induced in a vein both by active contraction of the calf and by passive compression of the calf muscle; reflux, if present, followed relaxation of the calf muscle or release of compression. Active calf contraction was achieved by asking the patient to perform a single dorsiflexion of the ankle while standing with weight on the opposite limb, followed by relaxation. For examination of veins above the calf, passive compression was attained by rapid inflation to 140 mmHg of a 5-cm diameter pneumatic tourniquet placed on the widest circumference of the calf, followed by rapid deflation 3 s later. Similar inflation of a 5-cm tourniquet placed around the foot was used to examine veins at a lower level. To investigate incompetent perforating veins of the calf, active ankle dorsiflexion and passive calf compression above the perforator were used.

Initial screening was performed using colour imaging with cephalad and reflux flow being demonstrated respectively by red and blue colours within the vessel (these colours may be interchanged by the operator). As the lowest mean flow that may be demonstrated as a colour on the scanner using the 5-MHz probe is 9 cm/s, the vein under investigation was then examined for the presence of reflux using the Doppler waveform of the scanner. The assessment of reflux in a vein was performed twice in each case to increase the reliability of the diagnosis[11].

The deep veins of the thigh and superficial veins of the thigh and leg were scanned throughout their length. In the calf, the deep veins were scanned at sites that gave the best visualization. For the anterior tibial veins this was below the upper border of the interosseous membrane; for the posterior tibial and peroneal veins it was in the distal half of the leg. Of the perforating (communicating) veins, only those on the medial side of the leg below the knee were examined because previous studies have suggested that these are the most important in the pathogenesis of skin changes[3]. It was not possible to examine all perforating veins, which may number up to 100 per leg[12]. The gastrocnemius veins were also examined because reflux in these is an important cause of calf swelling and aching, and may be responsible for a 5 per cent false-positive rate for popliteal reflux using continuous-wave ultrasonography[13].

Reflux was taken to be present in a vein only if reverse flow of $>0{\cdot}6$ s duration was present, as normal valves require up to this time to close[14]. In the superficial veins and superficial femoral vein, incompetence was taken to be present if reflux was demonstrated in $\geqslant 50$ per cent of the length of the vessel; reflux in shorter lengths was defined as segmental. The common femoral and popliteal veins were considered incompetent if reflux was demonstrated below their respective junctions with the long saphenous vein, and the short saphenous and gastrocnemius veins. The deep calf veins were taken to be incompetent if reflux was demonstrated in any segment along their length, except at junctions with incompetent perforating veins. Perforating veins were considered incompetent if flow was from deep to superficial during active dorsiflexion of the ankle, followed by superficial to deep flow during relaxation of the calf muscle[15]. Incompetence was also taken to be present if there was flow from deep to superficial on passive compression of the calf; this method correlates well with ascending venography in the diagnosis of perforating vein incompetence[16].

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Table 1 *Reflux in 202 legs without skin changes of chronic venous insufficiency defined by Doppler ultrasonography with colour-flow imaging*

	Pattern of incompetence				
	Superficial veins	Deep veins	Gastrocnemius veins	Medial calf perforating veins	No.
Superficial incompetence					
	+ (segmental)				18
	+ (segmental)		+	+	4
	+				85
	+			+	25
Total					132 (65·3)
Deep incompetence					
		+		+	2
	+	+	+		1
	+	+		+	5
	+	+	+	+	2
	+	+			5
		+			1
		+	+	+	1
Total					17 (8·4)
Perforating vein incompetence					8 (4·0)
No reflux					45 (22·3)

Values in parentheses are percentages

Table 2 *Reflux in 98 legs with skin changes of chronic venous insufficiency defined by Doppler ultrasonography with colour-flow imaging*

	Pattern of incompetence				
	Superficial veins	Deep veins	Gastrocnemius veins	Medial calf perforating veins	No.
Superficial incompetence					
	+				17
	+			+	35
	+		+		2
	+		+	+	2
Total					56 (57)
Deep incompetence					
	+	+			3
	+	+	+		9
	+	+		+	12
	+	+	+	+	12
		+	+		1
		+	+	+	1
Total					38 (39)
Perforating vein incompetence					2 (2)
No reflux					2 (2)

Values in parentheses are percentages

Table 3 *Reflux in 25 legs with ulceration defined by Doppler ultrasonography with colour-flow imaging*

	Pattern of incompetence				
	Superficial veins	Deep veins	Gastrocnemius veins	Medial calf perforating veins	No.
Superficial incompetence					
	+				3
	+			+	9
	+		+		1
Total					13 (52)
Deep incompetence					
	+	+			3
		+		+	2
	+	+		+	3
	+	+	+		3
		+	+	+	1
Total					12 (48)

Values in parentheses are percentages

Results

A total of 300 limbs in 153 patients, comprising 85 women and 68 men, were investigated. The median age was 50 (range 17–83) years. Of the 300 limbs, 202 had no skin changes at the time of investigation; 98 had skin changes of chronic venous insufficiency, of which 25 had venous ulceration.

Of the 202 legs without skin changes, 20 were normal control limbs of patients with no symptoms or signs of venous disease; 15 of these had no venous reflux on duplex scanning with colour-flow imaging. Of the remaining five 'normal' control limbs, two had isolated medial perforating vein reflux and three segmental superficial reflux. In patients with venous disease in the opposite leg, 57 limbs were clinically normal of which 27 had reflux on duplex scanning.

The distribution of venous reflux in limbs without skin changes, which includes the normal control limbs and the 'normal' limbs of patients with unilateral venous disease, is given in *Table 1*. Limbs are grouped according to the presence of reflux in the superficial, deep and communicating venous systems, or in a combination of these. The distribution of reflux is shown for legs with skin changes in *Table 2* and for those with venous ulceration in *Table 3*.

Discussion

Superficial vein incompetence has been reported to be important in the aetiology of skin ulceration[1,17]. The accurate diagnosis and differentiation of superficial and deep vein reflux is difficult, but the advent of duplex scanning and colour-flow imaging has allowed examination of individual veins for reflux, thus facilitating the diagnosis of superficial and deep incompetence. The present study confirmed the high incidence of superficial reflux, with 52 per cent of limbs with ulceration and 57 per cent of those with skin changes having superficial without deep vein incompetence, although 77 per cent of ulcerated limbs with superficial incompetence also had associated gastrocnemius or medial perforating vein reflux. This is in agreement with the findings of McMullin *et al.*[18], who demonstrated that two-thirds of patients presenting with symptoms of chronic venous insufficiency, lipodermatosclerosis, ulceration and eczema had only superficial vein insufficiency. However, the incidence is higher than that found by Sethia and Darke[1], who reported that 28 per cent of limbs with ulceration had superficial and perforating vein reflux in the absence of deep reflux, although this was based on investigation with ascending and descending venography rather than duplex scanning. Raju[19] investigated 147 limbs 'clinically suspected of venous insufficiency' using a combination of Doppler ultrasonography, photoplethysmography and venous pressure measurements. He found no isolated superficial vein insufficiency, isolated deep vein insufficiency in 77 per cent of limbs, and combined superficial and deep reflux in 23 per cent, although no differentiation was made between limbs with and without skin changes nor was the presence of perforating vein reflux addressed. The present study demonstrates an overall incidence of deep vein reflux of 18·3 per cent, whether alone or combined with reflux elsewhere and irrespective of skin changes. Some 16·3 per cent of limbs had combined superficial and deep reflux, regardless of the presence of skin changes but, unlike the study by Raju[19], only one limb without skin changes had isolated deep vein incompetence. It should be noted, however, that the population in the present study was selected in the sense that the patients were taken from a specialist venous clinic and included secondary and tertiary referrals.

This study has identified that a number of limbs have reflux only in segments of superficial veins. Sarin *et al.*[20] also demonstrated that flow in medial calf perforating veins may occur both from superficial to deep and from deep to superficial veins in clinically normal limbs, suggesting that 'reverse' flow may not always be abnormal. In the light of these findings, a population study of normal limbs using duplex scanning is required to assess the normal direction of venous flow in individual veins of the lower limb.

In the present study, the most reliable method of inducing deep to superficial flow in an incompetent perforating vein was active contraction of the calf muscle achieved by dorsiflexion of the ankle, with similar flow patterns to those demonstrated by Bjordal[15] using active contraction of the calf muscle being observed. Passive calf muscle contraction was also used, as this method correlates well with ascending venography in the diagnosis of perforating vein incompetence[16]. However, in view of the findings of Sarin *et al.*[20] that deep to superficial flow may occur in clinically normal limbs and that the presence of 'reverse' flow may alter depending on the site of compression, the diagnosis of perforating vein incompetence must be interpreted with caution, irrespective of the method used for diagnosis.

Negus and Friedgood[2], using combined examination, Doppler ultrasonographic testing and operative findings, reported that the incidence of isolated perforating vein reflux in 109 limbs with ulceration was 60 per cent; they demonstrated perforating vein reflux and deep vein incompetence in the remaining 40 per cent of limbs. This is in contrast to the present study, in which 60 per cent of limbs with ulceration had perforating vein incompetence, but this was always in combination with deep or superficial vein incompetence. No legs had ulceration with isolated perforating vein reflux, although 2 per cent of those with skin changes other than ulceration did have such isolated reflux. The incidence of perforating vein reflux in legs with ulceration in the present paper is lower than in most other studies, which have reported a value of between 71 per cent[21] and 100 per cent[22]. In the present study, only the medial calf perforating veins were examined (these have been shown to be the most important in the pathogenesis of skin changes[3]) and incidence data, therefore, do not take into account perforators on the lateral side of the calf, which would explain this discrepancy. This study has also demonstrated a higher incidence of gastrocnemius vein reflux combined with deep vein reflux in limbs with skin changes (23 per cent), compared with those with no such changes (2·0 per cent), suggesting that gastrocnemius vein in combination with deep vein incompetence is also important in the development of skin changes. In limbs with ulceration, a total of 20 per cent had gastrocnemius vein reflux, whether combined with superficial or deep incompetence.

In summary, superficial vein incompetence is an important aetiological factor in the development of skin changes. There is, however, an increased incidence of deep vein reflux and a higher incidence of perforating vein reflux in limbs with such changes, indicating the significance of these in the development of skin complications. The incidence of superficial reflux, whether isolated or combined with reflux in the perforating or gastrocnemius veins, in limbs with skin changes of chronic venous insufficiency is higher than that reported in many previous studies.

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Paper accepted 31 October 1992

Announcement

The Vascular Surgical Society of Great Britain and Ireland

The Annual General Meeting of the VSS this year will be held at the Royal Northern College of Music in Manchester on 18 and 19 November. Following receipt of a generous offer of sponsorship by The British Journal of Surgery Society, Council has decided that two separate prizes will be awarded for papers presented at the AGM.

The British Journal of Surgery Prize will be awarded for the best paper presented by a surgeon in training on basic or laboratory-based vascular research. The Founder's Prize will be awarded for the best paper presented by a surgeon in training on clinical research. The value of each prize is £500.

Further information about eligibility and instructions for entering will be circulated with the abstract and registration documents for the meeting.

P. L. Harris
Secretary
Vascular Surgical Society
of Great Britain and Ireland

Surgical workshop

Br. J. Surg. 1993, Vol. 80, June, 729–730

New needle to simplify removal of impalpable breast tumours

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Screening mammography has revealed increased numbers of impalpable abnormalities requiring localization and removal[1]. Hookwire localization is the preferred method in assisting such removal, although it is not a new approach[2]. Ultrasonography is also used, with a 'double-dye' technique; these two methods have been widely reported[3]. Ultrasonography is now used less in aiding removal of impalpable tumours, whereas the success of hookwire localization has resulted in this procedure becoming common practice. It is carried out in most hospitals in which mammographic facilities are available. The rapid and widespread introduction of the technique means that most consultant surgeons and radiologists are self-taught. If the number of cases per surgeon is low, the 'learning curve' will be long.

A problem associated with hookwire localization is that, no matter how experienced the radiologist, the tip of the wire may not always be placed exactly in the target (*Figure 1*). The surgeon must first identify the tip of the wire (hook) and then proceed in the presumed direction of the abnormality, which may be as far as 15 mm away.

Surgical technique

A simple solution to this problem is now available with the introduction of a graduated localization wire and needle (William Cook Europe, Letchworth, UK) plus an improved fibre-free localization card to avoid histological sampling error[4]. The wire facilitates accurate removal of the target with the minimum loss of surrounding breast tissue.

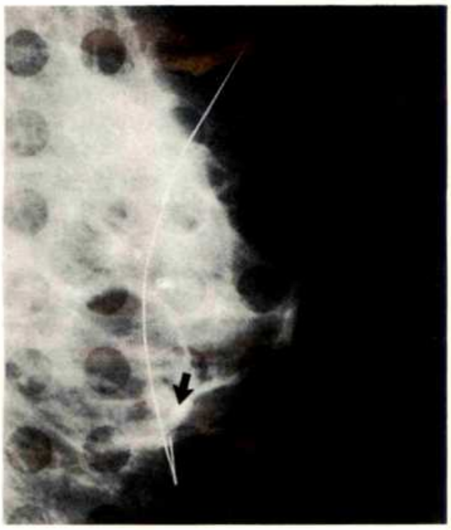

Figure 1 *The tip of the wire is approximately 15 mm beyond the 7-mm target (arrow), an invasive carcinoma adjacent to an area of ductal carcinoma* in situ

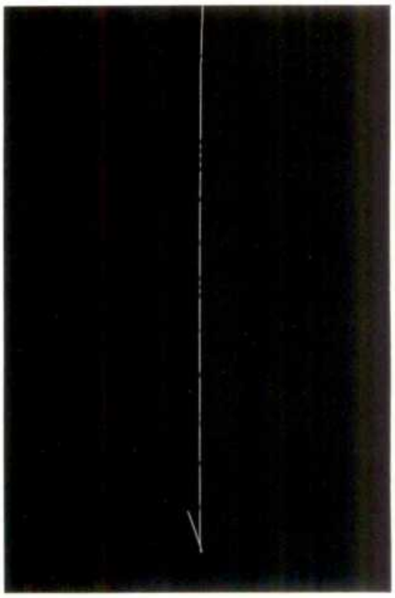

Figure 2 *Localization wire showing graduations every 1 cm with multiple rings every 3 cm*

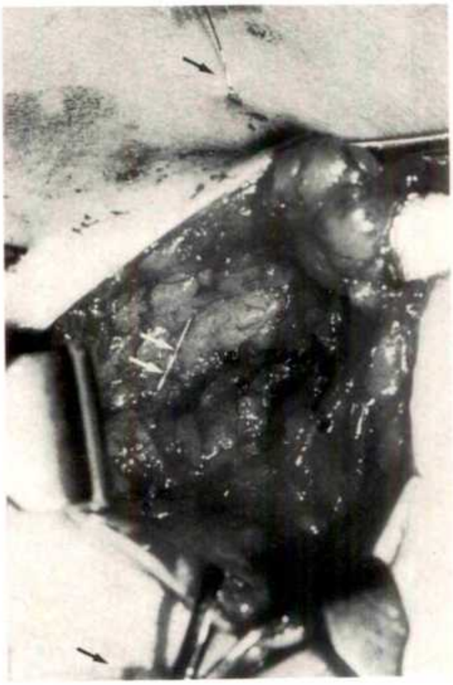

Figure 3 *The surgeon visualizes two circular markings on the wire exposed at operation (white arrows), indicating that the wire tip is 3 cm beyond this point. The wire entry point and nipple (black arrows) are also shown*

The main problem for the radiologist seeking accurate localization is to position the tip of the wire as close as possible to the target without over-running or stopping short of this area. The main problem for the surgeon occurs when the tip of the wire is positioned past the lesion, since it is then necessary to incise breast tissue across the target down the hookwire tip and then return the required distance to remove the target. The tissues will therefore be distorted, making removal of the target more difficult. The new guidewire eliminates these problems. It is calibrated with rings every 1 cm (*Figure 2*), which extend from the tip for 9 cm. When the breast is incised and the wire displayed, it is a simple matter for the surgeon to know the exact relationship of the exposed area of wire from the tip, even though the latter is hidden in the breast tissue. For example, if three black rings are seen, the position

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is 6 cm from the tip. More importantly, if the films show that the tip of the localization wire is approximately 2 cm beyond the target then, for the surgeon visualizing the wire (*Figure 3*), it is no longer necessary to estimate how far 2 cm might be from the concealed wire tip. The wire is followed until the 3-cm mark is revealed (i.e. two black rings), and excision of a small area of breast tissue to include the target is carried out.

Success assumes accurate localization in the plane of approach, which is reasonable since this is the easiest plane to localize if the radiologist ensures that the needle is at right angles to the calibration plate and that the entry point is correct. The greatest problem has been to predict how far to advance the needle without going beyond the target, and the new device is of maximum assistance in this respect. The radiologist now needs to make sure only that the wire tip does not lie short of the target, which can be over-run deliberately, knowing that the calibration will accurately guide the surgeon to the lesion.

Results

The wire has been used on six patients. A lateral radiograph was carried out in each case. The three surgeons involved all reported less tissue destruction in the target area, faster but accurate removal of the target and less normal tissue excised. In no case was a second wire necessary, and time in the radiology department was slightly reduced. However, the overall operating time was approximately the same, and in one patient was slightly longer as the hook was well past the lesion, requiring the wire to be cut with removal of the target and then removal of the hook.

This early experience demonstrates the major advantage of the new guidewire to be easier, accurate localization and removal of an undisturbed target, giving a 'clean' specimen with less normal tissue removed. It is also clear that second wire procedures will be rare, thus reducing radiation exposure to the breast.

Acknowledgements

The authors are grateful to Dr Stuart Field for assistance.

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Paper accepted 14 November 1992

Announcement

The British Journal of Surgery Society SRS Prize

The British Journal of Surgery Society is to make a generous annual donation of £500 to the Surgical Research Society to be used as a prize. The Committee of the SRS, on behalf of its membership, is pleased to acknowledge the gift with gratitude.

The SRS Committee has decided that the prize will be awarded for the best paper published in the *BJS* that originates from an SRS presentation in the preceding year. The Committee of the SRS will judge these papers at its January meeting and the prize will be announced and presented at the dinner of the SRS.

The SRS is pleased to maintain close ties with the Journal. Two months each year are special SRS issues and contain most of the papers from presentations made to the SRS. It is hoped that this prize will encourage more presenters of SRS papers to prepare manuscripts without detracting from the principle of the SRS to enjoy receiving reports of work in progress. Papers not making publication in the SRS issues *will not be ineligible* and the winner of the Patey Prize *may* submit a paper and be equally eligible. It should be noted that any paper submitted as a result of presentation to the SRS passes through the same rigorous process of referee analysis and editorial criticism by the Journal; publication is not guaranteed.

SRS authors should identify the January or July meeting of the presentation on the submitted manuscript. Papers will automatically be collected and reviewed for the prize. Those already published in 1993 issues will automatically be included for consideration of the prize to be awarded for the first time in January 1994.

'Thank you' to The British Journal of Surgery Society for fostering and encouraging surgical research.

J. R. Farndon
Honorary Secretary
Surgical Research Society

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731–733

Safe margins in the excision of primary cutaneous melanoma

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A group of 434 patients treated for primary cutaneous melanoma over an 18-year period by a policy of selective excision margins based on clinical estimation of tumour thickness was studied prospectively. Clinical assessments of tumour as impalpable, palpable but not overtly nodular, and nodular correspond to thicknesses of $\leq$0·75, 0·76–1·49 and $\geq$1·50 mm respectively. From 1971 to 1987, 330 patients were treated with excision margins of 1, 2 and 3–5 cm based on these respective ranges. During 1988 and 1989, 104 patients were treated after reduction of the maximum width of excision to 2 cm. The overall local recurrence rate was 11 of 434 patients (2·5 per cent), with no recurrence in melanoma $\leq$0·75 mm thick and no increase in the local recurrence rate after reduction of the maximum margin from 3 to 2 cm. A policy of 2-cm clearance for palpable and nodular melanoma and 1 cm for impalpable lesions is recommended. Any further reduction must be tested prospectively.

The optimum excision margin for primary cutaneous melanoma from oncological and cosmetic points of view remains controversial. It was accepted that a surgical excision margin $\geq$5 cm was the treatment of choice[1] but since 1970, when Breslow[2] introduced the concept that prognosis was related to tumour thickness, the dogma of wide excision has been challenged[3,4]. Adequate local control after conservative excision of thin melanoma has been reported[5–10]. Although a 1-cm margin is now widely accepted as adequate for thin (< 1 mm thick) melanoma, the minimum clearance necessary for thicker lesions remains unclear.

The results of a selective policy of excision based on clinical assessment of tumour thickness using margins of 1, 2 and 3 cm for tumour groups of increasing thickness were reported[11] in 1985. It was demonstrated that, in terms of recurrence, the maximum excision margin necessary to achieve local control could confidently be reduced to 3 cm in melanoma $\geq$1·50 mm thick and that tumour thickness could be estimated accurately by preoperative clinical assessment. The effect of a further reduction in the maximum width of excision to 2 cm is presented.

Patients and methods

A group of 434 patients undergoing definitive treatment for primary cutaneous melanoma under one surgical team between 1971 and 1989 was studied prospectively. The main characteristics of patients are shown in *Table 1*.

Treatment policy

Lesions were classified before operation into one of three groups[11]: impalpable, palpable but not overtly nodular, and nodular. In general, tumours in these three groups fell into the histological thickness ranges $\leq$0·75, 0·76–1·49 and $\geq$1·50 mm respectively. From 1971 to 1987, 330 patients were treated with excision margins of 1, 2 and 3–5 cm according to clinical estimation of tumour thickness (group 1). During 1988 and 1989, a further 104 patients have been treated with a 1-cm margin for impalpable tumours and a 2-cm margin for palpable lesions (group 2). These 104 patients have now been followed for a minimum of 2 years. The margins described are minimum clearances and were observed laterally and distally, an extra 1 cm being taken in the direction of the draining lymphatics if this could be done without affecting the cosmetic result. This is generally the case on a limb, where a longitudinal elliptical excision is performed. Deviation from the policy margins was recorded as the smallest clearance achieved. The subcutaneous fat was cleared to the deep fascia, which was conserved, and the wound irrigated with a cytotoxic solution of 1:5 buffered sodium hypochlorite. Skin closure was achieved using multiple layers of polypropylene[12], flaps or skin grafting as appropriate. Routine elective lymphadenectomy was not performed.

Follow-up

All patients were followed prospectively in a dedicated clinic. A full physical examination was always performed, but investigations carried out only when clinically indicated. Patients with tumours $\leq$0·75 mm thick were seen annually; all others were seen at 2-monthly intervals for the first 2 years, 3-monthly for years 3 and 4, 4-monthly for year 5 and annually thereafter.

Local recurrence was defined as that within the excision scar or graft site irrespective of whether or not it was the site of first recurrence, as this most adequately reflects completeness of excision. Recurrence within 5 cm of the graft has also been analysed. All recurrence was proven histologically or cytologically. The median follow-up was 120 (range 24–228) months.

Table 1 *Details of 434 patients with primary cutaneous melanoma*

	Group 1 (n = 330)	Group 2 (n = 104)
Sex		
M	90 (27·3)	33 (31·7)
F	240 (72·7)	71 (68·3)
Site		
Head or neck	61 (18·5)	17 (16·3)
Trunk	67 (20·3)	26 (25·0)
Lower limb	160 (48·5)	33 (31·7)
Upper limb	42 (12·7)	28 (26·9)

Values in parentheses are percentages

Table 2 *Distribution of tumour thickness*

Thickness (mm)	Group 1 (n = 330)	Group 2 (n = 104)
$\leq$0·75	112 (34·0)	45 (43·3)
0·76–1·49	60 (18·2)	20 (19·2)
$\geq$1·50	158 (47·9)	39 (37·5)

Values in parentheses are percentages

Presented to the Association of Surgeons of Great Britain and Ireland in Jersey, UK, April 1992

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Table 3 *Details of local recurrence*

Site	Breslow thickness (mm)	Minimum clearance (cm)	Time to recurrence (months)			Survival (months)	
			Local	Regional	Systemic	Alive	Dead
Neck	3·70	3·5	8	4	11	—	12
Neck	7·00	2·5	13	—	13	—	19
Face	1·92	0·5*	70	—	—	176	—
Face	2·26	2·0	55	33	57	—	62
Face	9·90	2·0†	12	12	14	—	30
Foot	1·40	2·0	47	21	60	—	60
Ankle	7·40	4·0	8	19	19	—	22
Calf	2·50	3·0	11	17	—	54	—
Trunk	3·10	4·0	42	49	56	—	62
Trunk	6·00	5·0	9	—	16	—	20
Trunk	3·30	3·0	3	1	3	—	6

*Initial pathological misdiagnosis as benign; †group 2. Times are from definitive treatment of the primary tumour

Results

A predominance of women was seen in both groups (approximate ratio 2:1), a finding in keeping with the distribution of melanoma in the UK. Melanoma of the limb was seen most commonly, with a higher proportion in group 1. The maximum incidence occurred between 41 and 70 years of age, accounting for approximately 60 per cent of primary tumours in both groups. Tumour thicknesses in the two groups are shown in *Table 2*. Lesions ⩾1·50 mm thick were more common in group 1, being present in 158 of 330 patients (47·9 per cent) *versus* 39 of 104 (37·5 per cent) in group 2, the result of an increased rate of detection of thin melanoma in recent years.

A total of 11 local recurrences were detected: ten (3·0 per cent) in group 1 and one (1·0 per cent) in group 2. If the definition of local recurrence is expanded to include that within 5 cm of the scar or graft there were 17 recurrences (5·2 per cent) in group 1 and two (1·9 per cent) in group 2. Primary tumour thickness was the main predictor of recurrence; in neither group was local recurrence detected in tumours ⩽0·75 mm thick and in only one of thickness 0·76–1·49 mm (*Table 3*). The mean time to recurrence was 25·3 (range 3–70) months, but the median was 12 months and 64 per cent were detected by 13 months.

Local recurrence was seen most commonly in the group of patients with primary melanoma ⩾1·50 mm thick: nine of 158 (5·7 per cent) in group 1 and one of 39 (3 per cent) in group 2. This decrease in frequency of local recurrence as maximum clearance decreased suggests that the selective policy had not compromised outcome. Since the median time to recurrence was 12 months and nearly two-thirds of recurrences were seen by 13 months, longer term follow-up is unlikely to demonstrate an adverse effect in terms of late recurrence. The median follow-up in group 2 is currently 3·5 years.

Discussion

It was proposed by Sampson Handley[1] that centrifugal spread was the mechanism underlying dissemination of malignant melanoma. However, it is now considered that micrometastases that have developed before surgical excision are responsible for later recurrence and their likelihood can be predicted from the thickness of the melanoma[2,3,13]. Both retrospective and prospective studies have demonstrated that overall survival is related to the biological characteristics of the primary tumour, most importantly thickness at presentation, and that the extent of surgical margins has little bearing on this[3–10,14].

The major rationale for 'adequate' margins, therefore, is local control but local recurrence is determined largely by the biology of the tumour and, in thick melanoma, may not be prevented even by extremely wide margins[6,14]. A randomized trial of 1-cm *versus* 3-cm margins for melanoma up to 2 mm thick did not show any statistically significant difference in either local recurrence rate or overall survival[10,11]. The authors cautioned that the only local recurrences were in melanomas 1–2 mm thick, which were treated with a 1-cm margin. Longer follow-up may resolve the issue. Although a 1-cm margin is widely accepted as adequate for thin melanoma (<1 mm thick), the minimum clearance required for local control of thick tumours has not been established. The trend in melanoma surgery has been toward a cautious retreat from arbitrarily wide margins that were supported by few scientific data[3–7,9–11,14]. In the present study, a reduction from 3 to 2 cm in the margin for thick melanoma was not accompanied by either decreased survival or an increase in the local recurrence rate, regardless of the definition of such recurrence.

If there is no benefit from margins >2 cm, the advantage of the reduced margin is clear. In a previous study[12], 76 per cent of 2-cm excision wounds could be closed directly using the multilayer polypropylene technique, compared with 33 per cent of 3-cm wounds. Apart from functional considerations, Cassileth *et al.*[15] have demonstrated that the indentation left following split skin grafting is the cosmetic defect that causes most distress after melanoma excision.

The following guidelines are suggested: impalpable tumours (<1 mm thick) should be excised with a 1-cm margin; and palpable or overtly nodular lesions (⩾1 mm thick) can be excised safely with a 2-cm margin, which can be reduced to 1 cm in the head and neck to conserve central anatomical features such as the eye or nose. This policy will allow the vast majority of melanoma excision wounds to be closed by simple suture, with flap or skin graft repair rarely being necessary. A prospective trial would show whether a further reduction from this upper 2-cm margin can be achieved with safety.

Acknowledgements

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Announcement

The Melanoma Study Group and British Association of Plastic Surgeons randomized controlled trial of excision width of cutaneous malignant melanoma of depth ⩾2 mm

Does a greater width of excision of malignant melanoma confer benefits in terms of lower local and metastatic recurrence rate? A 1-cm excision may generally be performed under local anaesthesia as an outpatient procedure with primary skin closure whereas a 3-cm margin requires general anaesthesia, inpatient care and skin grafting or other means of reconstruction.

To address such issues, The Melanoma Study Group and British Association of Plastic Surgeons are undertaking a randomized controlled trial of 1-cm *versus* 3-cm excision margins for cutaneous malignant melanoma of depth ⩾2 mm. The trial aims to assess the effect of excision margin on local and in-transit recurrence, regional lymph node and distant metastasis, and patient survival.

To be eligible, patients must have primary single localized malignant melanoma of depth ⩾2 mm not of the head or neck, fingers, toes, soles of the feet or palms of the hand. They must be over 18 years of age, not pregnant if female, consent to the study and be available for follow-up. Patients must have no previous history of cancer and not be receiving immunosuppressive or adjuvant therapy.

Tumours of this depth are uncommon; an individual surgeon may see no more than two or three per year. Surgeons who do not see many melanomas may still make an invaluable contribution; all are invited to join the study. For further information and a copy of the protocol please contact: Mr J. Meirion Thomas, Consultant Surgeon, Royal Marsden Hospital, Fulham Road, London SW3 6JJ. Telephone: 071 352 2269. Facsimile: 071 259 9552.

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Br. J. Surg. 1993, Vol. 80, June, 734–736

Purse-string suture for stapled oesophagogastric anastomosis: hand-sewn *versus* automatic

An automatic purse-string device was compared with the traditional hand-sewn method in stapled oesophageal anastomosis. Fifteen greyhound dogs underwent distal oesophagectomy with stapled gastro-oesophageal anastomosis; a purse-string suture was used to draw the distal oesophagus around the stapling device. The animals were randomized into group 1 ($n = 8$)*, in which the automatic device was used, and group 2* ($n = 7$)*, in which the oesophageal purse string was hand-sewn. The automatic device failed to incorporate the oesophageal mucosa and submucosa reliably into the anastomotic staple line. There were five defective anastomoses in group 1 and none in group 2* ($P = 0{\cdot}037$)*. Anastomotic bursting pressures were significantly reduced in group 1 compared with group 2 (median (range) 47 (22–110)* versus *82 (68–88) mmHg,* $P = 0{\cdot}032$)*. Within group 1, a significant difference in bursting pressure existed between complete anastomoses and those in which the mucosa was not fully incorporated (median (range) 75 (60–110)* versus *39 (22–50) mmHg,* $P = 0{\cdot}037$)*. Median (range) breaking strengths where anastomoses were incomplete were lower than where all layers were incorporated (1420 (1250–2220)* versus *1990 (1590–2475) g/cm,* $P = 0{\cdot}009$)*. This study questions the safety of the automatic purse-string device for oesophageal anastomosis when used in accordance with present recommendations. Further evaluation and possibly modification of either the instrument design or the methods recommended by the manufacturer for its use are warranted.*

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A critical step in the performance of stapled oesophageal anastomosis is the insertion of a temporary purse-string suture to draw the distal oesophagus around the stapling instrument. Precise insertion of this purse-string, with inclusion of all layers of the divided oesophagus, is desirable for anastomotic integrity. A recently introduced automatic purse-string instrument (Purstring; US Surgical, Norwalk, Connecticut, USA) has been advocated for purse-string insertion in the performance of stapled end-to-end oesophageal, intestinal and colorectal anastomoses[1]. The ability of the instrument to incorporate all oesophageal layers, and in particular the mucosa and submucosa, into the anastomosis satisfactorily was investigated.

Materials and methods

The experimental protocol was approved by the Department of Health (Ireland) and all experiments performed in accordance with Department of Health guidelines. Fifteen male greyhound dogs were anaesthetized with sodium thiopentone and ventilated with nitrous oxide, halothane and oxygen. Through an abdominal incision the distal 5 cm of oesophagus was excised and end-to-end gastro-oesophageal anastomosis performed using a 25-mm EEA (US Surgical) stapling instrument. In every case a temporary purse-string suture of 2/0 polypropylene was used to draw the cut end of the oesophagus around the jaws of the stapler. In group 1 ($n = 8$) the automatic purse-string device was used and in group 2 ($n = 7$) the oesophageal purse-string was hand-sewn.

The automatic device was used precisely in accordance with the manufacturer's recommendations. The jaws of the instrument were placed across the lower end of the mobilized oesophagus and when exact tissue placement was achieved the handles of the instrument were squeezed until they locked together. The oesophagus was then transected flush with the instrument. The device was opened and carefully removed, ensuring that the purse-string suture was completely released from the jaws without undue tension. The oesophagus was then held open using four Allis clamps while the head of the EEA device was inserted. The clamps were carefully applied so as to pick up all layers of the oesophagus proximal to the purse string and not to interfere in any way with either the staple line or the purse-string suture itself. The Allis clamps were then removed and one throw of a knot placed before tightening the purse string to draw the cut end of the oesophagus on to the shaft of the circular stapling gun.

Assessment of anastomotic integrity

The animals were immediately killed by lethal injection without waking from anaesthesia. The anastomosis was carefully excised including 5 cm of oesophagus proximally and 5 cm of stomach distally. Anastomotic integrity was assessed by gross examination and assessment of the rings excised by the anastomotic stapler. Anastomosis was deemed incomplete if the entire circumference did not incorporate mucosa.

Bursting pressures were measured on a standard length of the excised specimen. The proximal end was connected to a perfusor for injection of air at a constant rate and the distal end attached to a mercury manometer. The specimen was inflated under water and the appearance of air bubbles taken to indicate the anastomotic bursting pressure.

To measure breaking strength the entire anastomosis was cut into 1-cm wide longitudinal strips. Each strip was fixed at one end and subjected to increasing longitudinal tension. The tension at which the anastomosis disrupted was taken as the breaking strength. The breaking strength of every strip from each anastomosis was subjected to statistical analysis.

Statistical analysis

Comparison of anastomotic bursting pressures and breaking strengths was performed using the Mann–Whitney U test. Incidences of complete and incomplete anastomosis and tissue rings were compared using Fisher's exact test.

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Results

There were five incomplete anastomoses and six defective oesophageal tissue rings in group 1; neither defect was observed in group 2 ($P = 0.037$ and $P = 0.011$ respectively). One of the incomplete anastomoses had a defect through all layers of the oesophageal wall, while in the other four there was a failure to incorporate the oesophageal mucosa and submucosa into the staple line. Mucosal defects ranged in length from 15 to 100 per cent of the anastomotic circumference. Of the six defective oesophageal tissue rings, five exhibited incomplete incorporation of the mucosa and submucosa only. These tissue rings were entire in that they formed a full circle of the muscular layer and the defects in the mucosal and submucosal layers were evident only on close inspection. The sixth ring was defective through all its layers at the point in its circumference where the purse-string suture had been tied.

Anastomotic bursting pressures were significantly reduced in group 1 compared with group 2 (median (range) 47 (22–110) *versus* 82 (68–88) mmHg, $P = 0.032$). The five anastomoses in group 1 with mucosal defects showed the lowest bursting pressures, and these were significantly lower than pressures of anastomoses that were intact (median (range) 39 (22–50) *versus* 75 (60–110) mmHg, $P = 0.037$). The breaking strength of anastomotic strips at points where the mucosa was not incorporated was significantly less than where the anastomosis was intact (median (range) 1420 (1250–2220) *versus* 1990 (1590–2475) g/cm, $P = 0.009$). When the breaking strengths of all the strips, whether intact or defective, from the anastomoses were included, however, no significant difference was shown between groups 1 and 2 (median (range) 1915 (1250–2475) *versus* 2010 (1760–2250) g/cm, $P = 0.43$).

Two specific and separate technical faults with the automatic device were identified. Failure of the staples to pick up the oesophageal mucosa and submucosa reliably resulted in four defective anastomoses (*Figure 1*), while failure of the instrument to apply staples to the oesophagus at either end when compressed between the heads of the device resulted in one full-thickness anastomotic defect (*Figure 2*). The latter failure allows the purse string to slip off the cut end of the oesophagus at its 'loop' at one corner or at its knot at the opposite corner, resulting in exclusion of part of the oesophageal wall from the anastomosis.

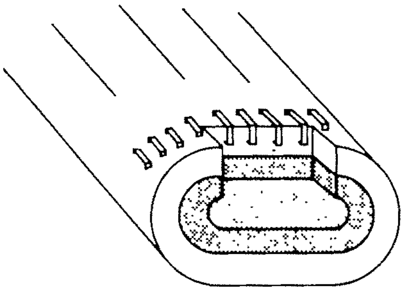

Figure 1 *Failure of the staples to penetrate the full depth of the oesophageal muscle layer. The submucosa and mucosa are not gripped by the staples and may not be incorporated in the anastomosis*

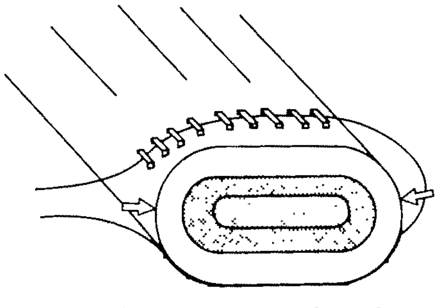

Figure 2 *Failure of the instrument to apply staples at either corner (arrows) when compressed in the jaws of the automatic purse-string device. This leaves a full thickness of the circumference that is not attached to the purse-string suture*

Discussion

The development of mechanical stapling devices for gastrointestinal anastomosis has yielded significant benefits. Operating times have shortened and, in general, the resulting anastomoses have been shown to be as safe as, if not safer than, those produced by the traditional hand-sewn methods[2]. Safety is of the utmost importance and the minimum requirement of these instruments is that they be at least as safe as the hand-sewn alternative. The automatic purse-string device used in the present study resulted in a high incidence of anastomotic imperfection compared with the hand-sewn technique and therefore failed to reach this minimum standard. Although the clinical relevance of measurements of anastomotic bursting pressure and breaking strength may be questioned, these observations further confirm the importance of the visible anastomotic defects. These results do not necessarily imply an increased anastomotic leakage rate, but they give sufficient grounds to question the use of the instrument in the oesophagus in the manner described by the manufacturer.

The present findings are not necessarily representative of the clinical situation, although the animal model of gastro-oesophageal anastomosis used has several points in common with human anastomosis. Histologically, as in the human, the canine oesophagus consists of mucosal, submucosal and muscular layers with a natural cleavage plane between the last two[3]. As in the human oesophagus, the mucosal and submucosal layers in the dog are not easily separated and the submucosa, which contains a considerable amount of connective tissue, has more tensile strength than the other oesophageal tissue layers[3]. In the greyhound the oesophagus is slightly smaller than in humans and the 25-mm EEA stapling device was selected in preliminary studies as it fitted the animal's oesophagus comfortably without causing undue tension to any layer of the oesophageal wall. When used exactly in accordance with the manufacturer's instructions, the automatic device does not reliably incorporate the oesophageal mucosa and submucosa into the staple line, resulting in clear anastomotic weakness. This defect may be specific to the oesophagus and no conclusions can be drawn concerning other sites in the gastrointestinal tract. Unfortunately, accurate apposition of the oesophageal and gastric muscle layers makes the defect in mucosal apposition invisible from outside the lumen and therefore not evident to the surgeon. Furthermore, the oesophageal tissue ring may appear intact because of the complete muscle layer and only careful examination will reveal the absence of the mucosal and submucosal layers through some or all of its circumference. Failure to attach the purse string at the loop or knot edges of the gut tube (*Figure 2*) could, in theory, occur when using the instrument to perform any intestinal anastomosis. Further investigation is required to determine the success rate with this instrument in performing colorectal and other intestinal anastomoses. Devitt[4] has highlighted this problem and has also noted the risk that staples may become detached because of the limited distance between the tissue edge and the row of staples. Devitt suggested that the oesophagus should not be cut flush with the jaws of the instrument, as recommended by the manufacturer. In the present study the oesophagus was transected flush with the instrument, but this problem was not encountered.

One possible solution to the problems encountered with the automatic device was described by Basso *et al.*[5] in relation to another purse-string applicator. Individual full-thickness sutures are inserted at intervals around the cut end of the oesophagus after insertion of the purse string and are used to assist insertion of the EEA stapler into the oesophagus and to ensure that all oesophageal tissue layers around its entire circumference are incorporated into the anastomosis.

Although most surgeons agree that the oesophageal mucosa and submucosa are essential to the integrity of an anastomosis, very few experimental studies have demonstrated this. The bursting pressures and breaking strengths measured here demonstrate significant anastomotic weakening when these oesophageal layers are not included in the anastomosis and emphasize their importance in oesophageal anastomosis in general.

The present study casts doubt on the safety of the automatic purse-string device when used in accordance with the manufacturer's recommendations. We suggest that further evaluation is warranted, possibly leading to modification of either the design of the instrument or the methods recommended for its use.

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Paper accepted 15 October 1992

Announcement

Association of Surgeons in Training (ASIT)

Membership of the Association is open to all trainees in every surgical specialty. Applicants should hold either the FRCS or CSIG Diploma.

The Association represents the views of members on all matters relevant to surgical training both at national and regional level and has representatives on most of the committees and boards that administer surgical training. Membership is free.

If you are not a member, please contact the Secretary, Bob Baigrie, at 7 Coverley Road, Oxford OX3 7ET, for details of membership, the Annual General Meeting and the name of your regional representative.

The next AGM will be held at St Bartholomew's Hospital on 17–18 September at the end of the Eurosurgery '93 Meeting.

R. J. Baigrie
Honorary Secretary
Association of Surgeons in Training

Br. J. Surg. 1993, Vol. 80, June,
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Proximal gastric vagotomy and anterior seromyotomy with posterior truncal vagotomy assessed by the endoscopic congo red test

The completeness of vagotomy following proximal gastric vagotomy or anterior seromyotomy with posterior truncal vagotomy was assessed prospectively in 48 patients using the intraoperative congo red test. Pentagastrin (6 µg/kg) was given subcutaneously before the assessment. An endoscope was passed into the stomach and 180 ml congo red solution washed over the gastric mucosa. Continuing acid production was indicated by the appearance of a black colour (pH < 3) 2 min after introduction of the dye. A grading system was adopted where grades I and II showed little black discoloration and grades III and IV showed increasing areas of discoloration indicating that further denervation was required. All 20 patients undergoing anterior seromyotomy with posterior vagotomy were classified as grade I. Fifteen of an initial 23 patients receiving proximal gastric vagotomy were grade III or IV. Following division of either the right gastroepiploic nerve or the posterior vagal trunk, 22 patients improved to grade I (16) or II (six). In the subsequent five proximal vagotomies, modification of the dissection produced grade I results. Anterior seromyotomy with posterior truncal vagotomy gave consistently complete vagotomy. The congo red test highlighted major differences in the adequacy of vagotomy achieved using various dissection techniques during proximal gastric vagotomy. The test is a useful, reproducible and simple intraoperative method for assessing the completeness of denervation.

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The development of highly selective vagotomy for chronic duodenal ulcer has greatly reduced the morbidity associated with partial gastrectomy or truncal vagotomy and drainage[1]. Unfortunately, a high rate of ulcer recurrence has been associated with proximal gastric vagotomy (PGV), which has brought this otherwise safe and uncomplicated procedure into disrepute[2]. Moreover, the lack of precise anatomical landmarks makes it difficult for surgeons in training to achieve adequate PGV. These problems led Taylor *et al.*[3] to develop the pylorus-preserving procedure of anterior seromyotomy with posterior truncal vagotomy in an effort to reduce the ulcer recurrence rate. An alternative approach to ensuring adequate vagotomy is to perform intraoperative intragastric pressure monitoring[4] or pH testing[5]. Donahue and colleagues[6] recently reported a modified endoscopic test that uses congo red as an indicator of acid production during PGV. In the present study, the intraoperative endoscopic congo red test was used in 48 patients undergoing either PGV or anterior seromyotomy with posterior vagotomy to determine its potential role in assessing the completeness of vagotomy.

Patients and methods

PGV was performed in 28 patients (six women) and anterior seromyotomy with posterior vagotomy in 20 patients (five women). The mean ages were 40 (range 15–67) and 42 (range 26–58) years respectively. There were two non-smokers in each group. With the exception of two patients with ulcers refractory to medical treatment, the indication for surgery was recurrent haemorrhage from a duodenal ulcer. All bleeding stopped on initial conservative therapy and patients then underwent early elective surgery. The study started in November 1989 with all patients receiving PGV However, in July 1990 the dissection performed for PGV was modified so that the lesser sac was entered through the gastrocolic ligament to allow improved dissection of the branches of the posterior nerve of Latarget; a more proximal clearance of the oesophagus was also effected. Anterior seromyotomy with posterior vagotomy was introduced in October 1990.

Patients did not receive H_2-receptor antagonist therapy for 24–48 h before surgery so as not to interfere with the congo red test. Towards the end of the surgical procedure, and 15–20 min before carrying out the test, a subcutaneous injection of pentagastrin (6 µg/kg) was given to stimulate maximal acid secretion. On completion of PGV or anterior seromyotomy before posterior vagotomy, an independent endoscopist performed the intraoperative congo red test. An Olympus GIF-Q10 endoscope (Olympus Optical, Tokyo, Japan) was introduced into the stomach. The stomach was irrigated with water and all excess fluid aspirated. After occlusion of the pylorus by the surgeon the endoscopist introduced 150–180 ml congo red solution (3 g/l) containing 0·5 per cent sodium bicarbonate solution into the stomach. Thorough contact of dye with the gastric mucosa was ensured and the solution then aspirated. The stomach was assessed at 2 min for the presence of black discoloration, indicating a pH < 3 and, therefore, continuing acid production. Such areas were noted for position (anterior or posterior, lesser or greater curvature, fundus or body of the stomach). An estimate of the relative surface area of the stomach showing a colour change was also made.

In 14 patients receiving PGV the right gastroepiploic neurovascular bundle was ligated and divided, and the congo red test repeated after an interval of 3–5 min. In a further ten patients the posterior trunk of the vagus was divided before repeating the test. Any alterations in the area of black colour change were recorded. For patients undergoing anterior seromyotomy, the congo red test was repeated after division of the posterior vagus nerve.

A grading system was devised, based on the apparent surface area showing black discoloration. For grade I classification ⩽5 per cent of the stomach was black, grade II 6–10 per cent, grade III 11–15 per cent and grade IV ⩾16 per cent. Grades I and II were considered acceptable.

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Statistical analysis was performed using the χ^2 test to compare results of the initial PGV (with no modification) with those of the completed seromyotomy with posterior vagotomy.

Results

On completion of the original PGV, two of 23 patients were assessed as grade I by the congo red test. Six patients were grade II, 11 grade III and four grade IV. In all cases the area of colour change was in the fundus and along the greater curvature of the body of the stomach. The first 14 patients improved in grade following right gastroepiploic ligation to a satisfactory level; patients of grade I (two), grade II (two), grade III (seven) and grade IV (three) became grade I (eight) and grade II (six). In a further nine patients additional posterior truncal vagotomy improved the findings from grade II (four patients), grade III (four) and grade IV (one) to grade I (eight) and grade III (one). In the patient classified as grade III there was no improvement and, despite further dissection, no other large nerve trunk could be identified; the right gastroepiploic bundle was therefore divided with an improvement to grade II on retesting. Using the modified dissection, the next five consecutive patients undergoing PGV were recorded as grade I.

Twenty patients were assessed on completion of seromyotomy before posterior truncal vagotomy. The areas of continued acid production were along the greater curve of the body of the stomach and, to a lesser extent, in the fundus. The initial grades for these individuals were: grade I (three patients), grade II (eight), grade III (six) and grade IV (three). Following the division of the posterior vagus nerve all patients were classified as grade I.

Anterior seromyotomy with posterior vagotomy produced a significantly greater reduction in the surface area of the stomach turning black than PGV ($P < 0{\cdot}0001$). The operating time for seromyotomy with posterior vagotomy was 45–65 (mean 55) min and for PGV 70–120 (mean 90) min ($P < 0{\cdot}01$).

Discussion

For patients with chronic duodenal ulceration, the advantages of PGV over partial gastrectomy or truncal vagotomy are well described. These include a reduction in postcibal syndromes and in postvagotomy diarrhoea and dumping. Although PGV is safe and free from major complications, ulcers recur at a rate of 6–30 per cent[7,8]. Such variation appears to be operator dependent[9] and has led to the use of intraoperative testing of the adequacy of vagotomy on completion of the surgical procedure. The Burge test[4], which measures the change in intragastric pressure on stimulation of the stomach wall, shows indirectly that if motor vagal fibres are intact then secretory fibres are also intact. The test, however, does not indicate where these fibres are and the equipment required is expensive and fragile. Similarly the Grassi[5] test, which uses a probe to measure the intragastric pH directly over the surface of the mucosa, is associated with temperamental, delicate and expensive equipment. Neither test has been found to add sufficient information to reduce the rate of recurrence of ulcers after PGV[10,11].

Donahue *et al.*[12] have pursued the use of the endoscopic congo red test during PGV and as a result have modified their operative technique. In the present study, the congo red test was used to detect the presence of a colour change related to continued acid production. The pattern of residual acid production was dependent on the operation performed and the surgical technique. After the standard PGV employed at the start of the study, 23 patients were found to have continued acid production in the fundus and along the greater curve. Using an empirical grading system only eight of these patients were considered to have undergone adequate vagotomy (grade I, two patients; grade II, six). Further division of the right gastroepiploic neurovascular bundle in 14 patients resulted in an improvement on retesting, with all patients now adjudged to have a satisfactory result (grade I, eight patients; grade II, six). This manipulation of the gastroepiploic nerves has bee advocated previously[13,14]. In the present study it was foun that the area generating residual acid is in the region innervate by the posterior vagal trunk. It seemed reasonable therefore t assess the effect of adding posterior truncal vagotomy to th PGV. In eight cases there were further improvements seen wit all patients becoming grade I. This modification resembles th operation of Hill and Barker[15].

The dissection performed for PGV was later modified an more closely followed the procedure described by Johnston an Wilkinson[16] and Goligher[17]. This involved a more extensiv dissection of the oesophagus and the angle of His, and enterin the lesser sac through the greater curve to approach th posterior nerve of Latarget. All five patients operated on in thi manner were recorded as grade I by the congo red test. Th alteration in technique demonstrates that one surgeon's highl selective vagotomy may be less than selective compared wit another's; this was obvious when viewed down the endoscop during the intraoperative test. Such variations in technique ma account for the widespread differences in ulcer recurrence rat following PGV reported in the literature.

The first step in anterior seromyotomy in the present stud was to identify the anterior vagus nerve, isolate it in a silk slin and then to identify the anterior nerve of Latarget going off t the lesser omentum. Radical dissection of the oesophagus wa then performed, similar to that of the oesophageal dissectio of a PGV, followed by seromyotomy as described by Taylor[18] Although the posterior vagal trunk was intact, many of it branches supplying the fundus and the left gastroepiploic vessel had already been divided. On assessing the stomach by the congo red test at this stage in the dissection it was not surprising to find a considerable degree of denervation had already bee accomplished; 11 patients were graded as satisfactory at thi time. Residual areas of innervation were mainly along the greater curve of the body of the stomach. By dividing the posterior vagal trunk, remaining acid production was virtually abolished. There seems little point, therefore, in adding right gastroepiploic ablation to the anterior seromyotomy and posterior vagotomy as suggested recently[19].

An advantage of anterior seromyotomy with posterio truncal vagotomy over PGV is a shorter operating time[20]. Thi was confirmed in the present series. Seromyotomy with posterior vagotomy also appeared to give a more consistent and effective vagotomy than PGV. However, this apparent advantage was lost following the introduction of the modified dissection for PGV.

Acid secretion studies were not performed in the present study. Previous work, however, has shown good correlation between congo red testing and acid secretion[6,21]. To date, no symptomatic recurrences have been detected but the follow-up is short. No patient has symptoms to suggest either dumping or postvagotomy diarrhoea.

In conclusion, the variation in completeness of vagotomy during PGV was demonstrated using the endoscopic congo red test. There being few opportunities to perform elective surgery for chronic duodenal ulceration, the endoscopic test offers a ready assessment of vagotomy for the surgeon in training, and encourages greater awareness of some of the pitfalls associated with vagotomies that preserve the pylorus. A more complete vagotomy reduces the chance of recurrent ulcer formation. The technique also allow rapid retesting after further division of nerve fibres as a final check on the procedure. The test is easy to perform, does not require specialized equipment, and adds little to the operating time. It has a useful role in the intraoperative assessment of the completeness of vagotomy.

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Paper accepted 10 October 1992

Announcements

Rhône–Poulenc Rorer Surgical Trainees Travel Award 1993

The Rhône–Poulenc Rorer Travel Award for Surgeons in Training is arranged for the Association of Surgeons in Training (ASIT) and the British Orthopaedic Trainees Association (BOTA). It is aimed to promote the exchange of information from surgical specialties across the international community.

A first prize of £1500 will be awarded to the trainee who, in the opinion of the judges, has written the most outstanding dissertation on any aspect of surgical oncology. A second prize of £750 will also be awarded.

This award is open to all trainees who are members of either ASIT, BOTA or the Irish Senior Registrars Group in Surgery.

The closing date for entry is 31 July 1993.

Davis and Geck ASIT Travelling Scholarships

These Scholarships have been created to assist in the cross-fertilization of ideas, skills and surgical techniques within the international surgical community. The Scholarships are open to all ASIT members and two winning candidates will receive either £1000 or £500 towards their costs. The recipients will be announced in September at the ASIT AGM. The Scholarships are not aimed at assisting papers to be read abroad but are to help members in gaining clinical experience by direct contact with surgeons overseas.

Applications (approximately 250 words) must include the proposed itinerary, purpose of visit and probable cost, and a letter of acceptance from the centre(s) to be visited. Application forms are obtainable from your local Davis and Geck representative or Bob Baigrie, Secretary of ASIT, 7 Coverley Road, Oxford OX3 7ET.

Applications must be in the hands of the Secretary by 31 August 1993.

R. J. Baigrie
Honorary Secretary
Association of Surgeons in Training

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740–744

Growth hormone therapy initiated before starvation ameliorates the catabolic state and enhances the protein-sparing effect of total parenteral nutrition

The effect of 7 days of subcutaneously administered bovine growth hormone (bGH) ($0\cdot2$ mg kg^{-1} day^{-1}; $n = 4$) or an equivalent volume of $0\cdot15$ mol l^{-1} saline ($n = 3$) on protein metabolism was assessed in lambs. The catabolic response to 48 h of starvation and subsequent hypocaloric total parenteral nutrition (TPN) was measured using primed constant intravenous infusions of [^{15}N]urea and [^{14}C]leucine. Following 48 h of starvation and 7 h of TPN, bGH-treated animals had a significantly decreased rate of net protein catabolism compared with controls (mean(s.e.m.) 2·4(0·2) versus 3·2(0·3) g kg^{-1} day^{-1}, $P < 0\cdot01$). The mean(s.e.m.) rate of whole-body protein catabolism was also significantly decreased in bGH-treated animals at 10·9(0·3) g kg^{-1} day^{-1} compared with 12·9(0·7) g kg^{-1} day^{-1} in saline-treated controls ($P < 0\cdot05$). In addition, the rates of net and whole-body protein catabolism decreased significantly ($P < 0\cdot05$) during the period of hypocaloric parenteral feeding to mean(s.e.m.) values of 2·3(0·2) and 8·6(0·6) g kg^{-1} day^{-1} respectively in bGH-treated animals. By contrast, in saline-treated controls net and whole-body protein catabolism continued to increase during hypocaloric parenteral feeding. There was a significant decrease ($P < 0\cdot05$) in the rate of [^{14}C]leucine uptake in tissues of the gastrointestinal tract, heart and diaphragm in bGH-treated animals compared with controls. These results demonstrate that daily administration of growth hormone decreases the catabolic response to a metabolic stress, resulting in the conservation of protein in the heart, diaphragm, gastrointestinal tract and musculoskeletal system by a primary anticatabolic action. In addition, growth hormone therapy initiated before induction of the catabolic state enhances the protein-sparing effects of TPN. Further study is justified to determine whether growth hormone therapy initiated before elective or urgent surgery in the nutritionally depleted patient may have a role in reducing the severity of the postoperative catabolic state, particularly in the patient in whom a complicated course is anticipated.

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Protein calorie malnutrition is common in hospital patients and has been detected in up to 50 per cent of those undergoing surgery[1]. A number of investigators have demonstrated that malnutrition results in an increased postoperative morbidity rate, with poor wound healing, impaired mobilization and reduced respiratory effort known to occur in the nutritionally depleted surgical patient[2,3]. However, the provision of preoperative nutritional support, usually total parenteral nutrition (TPN), in the nutritionally depleted patient has not decreased the incidence of postoperative complications[4]. This is consistent with data from a number of metabolic studies which have demonstrated that, although TPN optimizes the rate of whole-body protein synthesis in critically ill surgical patients, whole-body protein catabolism remains disproportionately high and these patients remain catabolic[5,6]. As a result, malnourished surgical patients are generally managed with an early operation and later nutritional support although it is now clear that the critically ill patient after surgery also remains catabolic in spite of aggressive parenteral nutritional support[6].

Recombinant human growth hormone (rHGH) has been used as an anabolic agent to enhance the protein-sparing effects of TPN in the critically ill. Several prospective trials[7–9] have shown that daily administration of rHGH for up to 7 days, in addition to TPN, is associated with a significant improvement in nitrogen balance after surgery in the stressed and catabolic patient, indicating that rHGH has a role in the metabolic management of these patients. However, there is evidence that rHGH is a useful anabolic agent in other less stressed populations, particularly children[10] and the elderly[11]. This suggests that the hormone may have a potential role as a preoperative anabolic agent, either alone or in addition to TPN, to optimize the status of the nutritionally depleted surgical patient who requires elective or urgent surgery.

The present study was designed to determine the effect of an elective course of growth hormone on whole-body and tissue protein metabolism in an animal model. The specific aims were to define: (1) the effect of a course of growth hormone in an unstressed host on the protein catabolic response to subsequent metabolic stress; (2) the effect of a course of growth hormone on the response to nutritional support following a period of

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metabolic stress; and (3) the mechanism of growth hormone activity in this context.

Materials and methods

All studies were performed in fully weaned cryptorchid crossbred male lambs, weighing 15–20 kg. Methods were approved by the Animal Ethics Committee at the University of Auckland.

Study design

Animals were studied for a total of 8 days. Recombinant bovine growth hormone (bGH; donated by American Cyanamid, Princetown, New Jersey, USA) 0·2 mg kg^{-1} day^{-1} ($n = 4$) or an equivalent volume of 0·15 mol l^{-1} saline ($n = 3$) was administered by subcutaneous injection at 08.00 hours for 7 days. The animals were kept in floor pens and allowed to feed *ad libitum* on a standard ruminant diet for the first 5 days of the study. They were then starved for 48 h. Daily blood samples were taken a minimum of 12 h after bGH administration for the determination of plasma insulin-like growth factor (IGF) 1 concentration throughout this 7-day period. On day 8, after 48 h of starvation, the lambs were placed in Pavlov slings and catheters placed percutaneously into both external jugular veins for the infusion of parenteral nutrition and isotopes, and for the sampling of blood. This experimental model has been described in detail elsewhere[12].

The animals then received a constant infusion of TPN for 12 h. Some 4 h after starting TPN a primed constant infusion of stable and radioisotopes was begun. Isotopic steady state was reached 3 h later (i.e. after 7 h of TPN) and plasma samples were then taken at hourly intervals to allow the determination of protein kinetics for the final 5 h of the study. After 12 h of parenteral nutrition the animals were killed by intravenous injection of 5 g phenobarbitone and samples of tissue collected by open dissection as described previously[12].

Radioisotopes

The isotopes were mixed under sterile conditions and administered as a primed constant infusion. [^{15}N]urea (Australasian Mass Analysis, Auckland, New Zealand) was infused at a rate of 10 μg kg^{-1} min^{-1} with a 450:1 priming dose. [^{14}C]leucine (Amersham Laboratories, Chalfont, UK) was administered at a rate of 7·5 nCi kg^{-1} min^{-1} after a 60:1 leucine priming dose.

Total parenteral nutrition

The TPN solution was made up on the day of administration. Protein was infused as a balanced amino acid solution (Synthamin 17; Travenol Laboratories, Sydney, Australia) at a rate of 1·5 g kg^{-1} day^{-1}. TPN supplied approximately half the caloric requirements of the growing lamb. Non-protein calories were made up of a 50:50 mix of dextrose and lipid (Intralipid 20; Kabi Pharmacia, Stockholm, Sweden) and were administered at a rate of 84 kJ kg^{-1} day^{-1}. This solution was made up with 0·15 mol l^{-1} saline to provide sufficient fluid for maintenance requirements. No extra electrolytes or trace elements were added to the solution.

Sample analysis

Blood samples were immediately chilled and centrifuged and the plasma frozen. Plasma glucose and free fatty acid (FFA) concentrations were determined as described previously[13]. Methods for the determination of plasma [^{15}N]urea and [^{14}C]leucine specific activity have been reported[12,13].

Tissue samples were initially blotted dry and then frozen in liquid nitrogen. They were later thawed and after extraction of fat the branched-chain amino acids (including leucine) separated using column chromatography. The leucine fraction was then separated using high-performance liquid chromatography and the specific activity of leucine in tissue determined as described previously[14].

Calculations

The rates of appearance of leucine (R_L) and urea (R_U) in plasma were calculated using the Steele equation or a modification of this as it applies to stable isotopes[15]. The rate of net protein catabolism (NPC) was derived as follows[13]:

$$\mathrm{NPC}\ (\mathrm{g\ kg^{-1}\ day^{-1}}) = \text{protein intake}\ (\mathrm{g\ kg^{-1}\ day^{-1}}) - \frac{R_U(\mu\mathrm{mol\ kg^{-1}\ min^{-1}}) \times 2\ \mu\mathrm{mol\ N\ per\ }\mu\mathrm{mol\ urea} \times 14\ \mu\mathrm{g\ N\ per\ }\mu\mathrm{mol\ N} \times 6{\cdot}25\ \mu\mathrm{g\ protein\ per\ }\mu\mathrm{g\ N}}{10^6\ \mu\mathrm{g\ per\ g} \times 60\ \mathrm{min\ per\ h} \times 24\ \mathrm{h\ per\ day}}$$

The rate of whole-body protein catabolism (WBPC) was determined from the rate of leucine appearance in plasma[14]:

$$\mathrm{WBPC}\ (\mathrm{g\ kg^{-1}\ day^{-1}}) = R_L\ (\mu\mathrm{mol\ kg^{-1}\ min^{-1}}) \times 2{\cdot}44$$

(allowing for 1440 min day^{-1} and 590 mmol leucine per gram protein). The fractional synthetic rate of protein (FSR) was determined from the specific activity of leucine in tissue:

$$\text{FSR in tissue (per cent per day)} = \text{change in [}^{14}\text{C]leucine tissue specific activity} \times \text{time (days)} \div \text{change in [}^{14}\text{C]plasma leucine specific activity}$$

Hormone assay

The plasma levels of IGF-1 were determined with a radioimmunoassay using a rabbit antiserum to its immunologically active component at a final titre of 1:150000 following extraction from plasma-binding protein using the acid–ethanol cryoprecipitation technique. This has been validated for sheep plasma[16].

Statistical analysis

Data from within-treatment groups were analysed using Dunnet's variation of a repeated measures analysis of variance. Comparisons between groups were made with two-way analysis of variance.

Results

Plasma hormone concentrations

Treatment with bGH increased ($P < 0{\cdot}01$) the mean(s.e.m.) daily plasma IGF-1 concentration to 600(27) ng ml^{-1} from a pretreatment value of 361(11) ng ml^{-1} during the 5 days of treatment and feeding *ad libitum*. Circulating levels of IGF-1 declined significantly ($P < 0{\cdot}05$) in both groups during the 48 h of starvation on days 6 and 7 of the study (*Figure 1*). During parenteral feeding, circulating IGF-1 concentrations were significantly higher in bGH-treated than control animals (*Figure 1*).

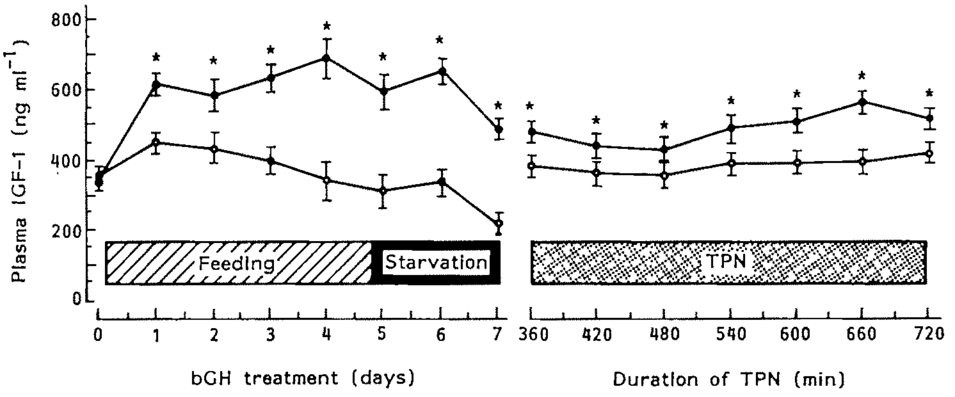

Figure 1 *Mean(s.e.m.) plasma insulin-like growth factor (IGF) 1 concentrations during feeding* ad libitum, *starvation and total parenteral nutrition (TPN) in bovine growth hormone- (bGH) (●) and saline- (○) treated animals.* *$P < 0{\cdot}05$ *(ANOVA)*

Fat metabolism

The mean(s.e.m.) concentration of FFAs in plasma was significantly increased ($P < 0{\cdot}01$) from 0·09(0·03) to 0·32(0·02) mmol l^{-1} following 5 days of bGH treatment and feeding *ad libitum*. There was no significant difference in the mean(s.e.m.) plasma FFA levels between days 1 and 5 of treatment in the control group (0·10(0·04) *versus* 0·18(0·04) mmol l^{-1}). Similarly there was a difference in the mean(s.e.m.) hourly plasma FFA concentration between the control and treatment groups during the 12 h of parenteral feeding (0·21(0·008) *versus* 0·23(0·009) mmol l^{-1}, $P < 0{\cdot}07$).

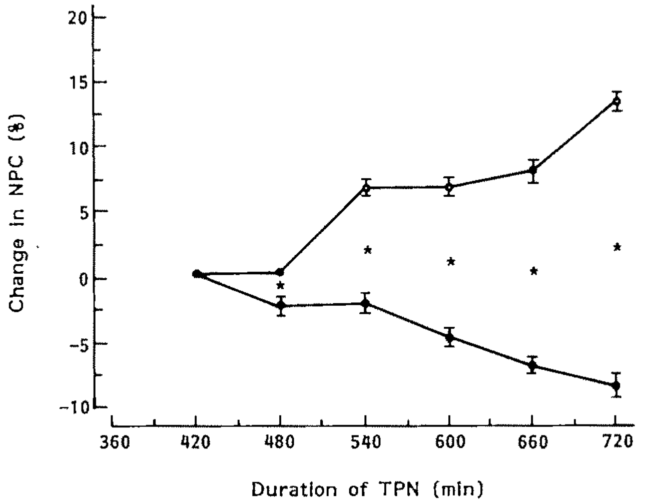

Figure 2 *Mean(s.e.m.) net protein catabolism (NPC) following 48 h of starvation and 7 h of total parenteral nutrition (TPN) in bovine growth hormone- (●) and saline- (○) treated animals.* *$P < 0{\cdot}05$ *(ANOVA)*

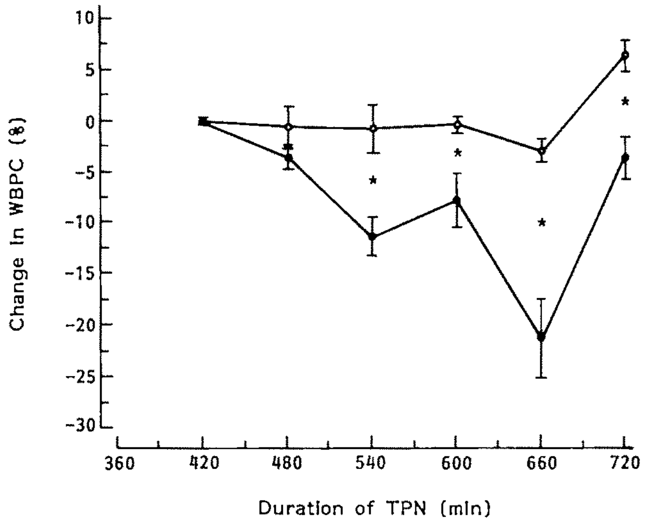

Figure 3 *Mean(s.e.m.) whole-body protein catabolism (WBPC) following 48 h of starvation and 7 h of total parenteral nutrition (TPN) in bovine growth hormone- (●) and saline- (○) treated animals.* *$P < 0{\cdot}05$ *(ANOVA)*

Glucose metabolism

The mean(s.e.m.) daily plasma glucose concentration was higher in bGH-treated than untreated animals during the 5 days of growth hormone treatment and feeding (4·1(0·8) *versus* 3·6(0·1) mmol l^{-1}, $P < 0{\cdot}01$). There was no difference in the mean(s.e.m.) hourly plasma glucose concentration between the two groups during the period of parenteral feeding (13·8(1·2) *versus* 13·2(0·6) mmol l^{-1}).

Protein metabolism

The mean(s.e.m.) rate of net protein catabolism was significantly decreased in bGH-treated compared with control lambs following 180 min of isotope infusion and 7 h of parenteral feeding (2·4(0·2) *versus* 3·2(0·3) g kg^{-1} day^{-1}, $P < 0{\cdot}01$). In addition, the rate of net protein catabolism in bGH-treated animals decreased significantly ($P < 0{\cdot}05$) to 2·3(0·2) g kg^{-1} day^{-1} during the period of parenteral feeding while there was a significant increase ($P < 0{\cdot}03$) in the rate in untreated controls (*Figure 2*).

The mean(s.e.m.) rate of whole-body protein catabolism was significantly less in bGH-treated animals compared with controls following 180 min of isotope infusion (10·9(0·3) *versus* 12·9(0·7) g kg^{-1} day^{-1}, $P < 0{\cdot}05$). The rate of whole-body protein catabolism did not change significantly in control animals during parenteral feeding. In bGH-treated lambs this rate decreased significantly from a mean(s.e.m.) of 10·9(0·3) to 8·6(0·6) g kg^{-1} day^{-1} following 660 min of parenteral nutrition (*Figure 3*).

In animals pretreated with bGH there was a significant decrease in the fractional synthetic rates of protein in all tissues sampled (*Figure 4*). This was most significant ($P < 0{\cdot}01$) in psoas muscle, diaphragm and kidney.

Discussion

The aim of this investigation was to define the effect of a course of growth hormone on the protein catabolic response to metabolic stress, the response to subsequent nutritional support, and the mechanism of the metabolic effect of growth hormone in this context. Although starvation does not result in the same metabolic derangements as surgery, this investigation did not attempt to reproduce the complex metabolic alterations accompanying operation; fasting is the most easily reproducible model of metabolic stress currently available. In addition, the administration of hypocaloric parenteral nutrition in the fasted state is a useful method for

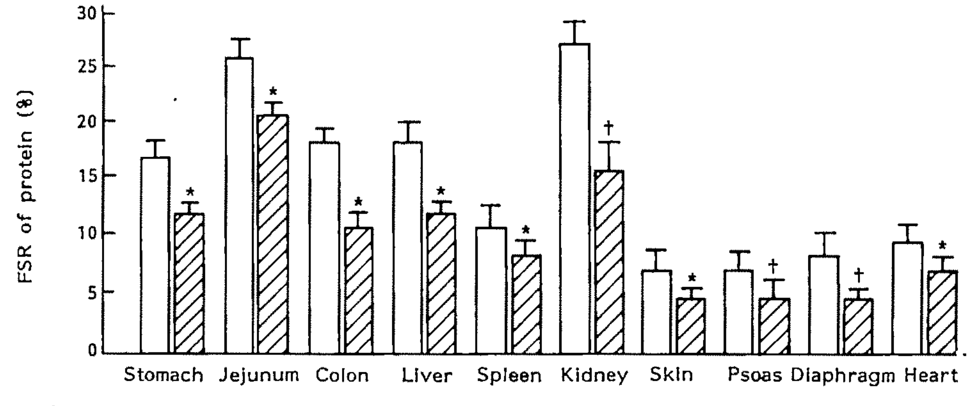

Figure 4 *Mean(s.e.m.) fractional synthetic rates (FSR) of protein in tissue following 48 h of starvation and 12 h of total parenteral nutrition in bovine growth hormone- (■) and saline- (□) treated animals.* *$P < 0{\cdot}05$; †$P < 0{\cdot}01$ *(ANOVA)*

assessing the responsiveness to TPN. Similarly, use of an animal model rather than a clinical investigation involving surgical patients enabled the study population to be carefully standardized and permitted the collection of a variety of tissues at the conclusion of the study for the determination of leucine uptake.

This investigation has demonstrated that pretreatment with bGH decreases the protein loss seen in healthy lambs following 48 h of starvation. This is associated with a decrease in the rate of leucine uptake in all tissues and a decrease in whole-body protein catabolism, suggesting that bGH acts primarily to reduce protein catabolism rather than to increase protein synthesis. Growth hormone treatment is known to increase lean body mass and it is therefore likely that bGH-treated animals had an increased muscle mass following 5 days of treatment and feeding *ad libitum*[17,18]. The decreased rate of catabolism seen in these lambs after starvation may therefore reflect a decrease in the absolute rate of protein loss or alternatively these animals may have lost a similar amount of protein to the untreated animals but have had a larger pool from which to lose it. However, following 48 h of starvation the rates of net and whole-body protein catabolism in bGH-treated lambs were 25 per cent less than in untreated animals and the rate of protein catabolism continued to decline throughout the period of parenteral feeding. This indicates that the absolute rate of net protein catabolism following starvation was decreased in bGH-treated animals. This anticatabolic effect of growth hormone is in contrast to the primarily anabolic effect observed after operation in patients given growth hormone[7].

Pretreatment with bGH not only decreased the protein loss seen after 2 days of starvation but enhanced the response to parenteral feeding at this time. Animals that received bGH supplementation were significantly less catabolic after 7 h of parenteral feeding. The increase in plasma glucose concentration seen in treated lambs represents relative insulin resistance and indicates that the improvement in the response to TPN is not the result of an insulin-mediated increase in tissue substrate uptake. Protein loss continued to decrease in bGH-treated animals during hypocaloric TPN, demonstrating that these were more responsive than saline-treated controls to nutritional support.

Overall, bGH therapy and TPN decreased protein loss by 30 per cent compared with animals treated with TPN alone; this was associated with a decrease in the tissue uptake of leucine consistent with a generalized decrease in protein turnover at a tissue level. This protein-sparing effect of growth hormone administration was most marked in the diaphragm and the psoas muscle. The increased morbidity rate associated with malnutrition is related to an increased incidence of bronchopneumonia resulting from poor inspiratory effort and delayed postoperative mobilization[2], so it is possible that preoperative administration of growth hormone might improve the convalescence of the nutritionally depleted patient.

Growth hormone administration also conserved tissue protein at all levels of the gastrointestinal tract; this has important implications for the healing of enteral anastomoses. A number of investigators have shown that exogenous growth hormone increases the collagen content of rat colon[19] and granulation tissue[20], while clinically Herndon *et al.*[21] demonstrated accelerated wound healing in children treated with growth hormone. In addition, growth hormone administration may also preserve the integrity of the mucosal barrier and so prevent bacterial translocation during periods of bowel rest and intravenous nutritional support. Other investigators[9] have noted fewer Gram-negative septic complications in a group of critically ill patients with sepsis treated with rHGH.

The mechanism of the observed anticatabolic effect of growth hormone is not clear; however, low levels of circulating IGF-1 are characteristic of malnutrition and critical illness[22]. It has previously been shown that supraphysiological doses of IGF-1 decrease protein catabolism and promote protein synthesis[12], while an acute reduction in the level of circulating IGF-1 is associated with an increase in protein catabolism[23]. The fall in plasma IGF-1 level observed in starvation or critical illness may provide a stimulus for an increase in protein catabolism to provide additional substrate for hepatic gluconeogenesis. In the present investigation bGH-treated animals showed a consistently raised plasma concentration of IGF-1 and pretreatment with growth hormone before a catabolic insult may attenuate the fall in circulating IGF-1 level and the resulting increase in protein catabolism. In addition, the higher levels of IGF-1 present in growth hormone-treated animals following starvation may enhance the response to nutritional support.

The use of rHGH in conjunction with nutritional support in patients with severe sepsis after operation is now under intensive clinical investigation. Although it is not possible to infer that a course of growth hormone before operation will improve clinical outcome, the present investigation indicates that growth hormone does attenuate the catabolic response to stress and prevents the loss of protein from a number of vital organ systems. Further work is now justified to determine whether the administration of growth hormone may have an important and currently unrecognized role in the preoperative management of the malnourished patient undergoing elective or urgent surgery.

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Case report

Br. J. Surg. 1993, Vol. 80, June, 744

Unusual case of large bowel obstruction

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The clinical picture of colonic obstruction results from a variety of causes that may be divided into mechanical and non-mechanical. An unusual case is presented of non-mechanical large bowel obstruction occurring in association with isolated gangrene of the vermiform appendix.

Case report

An 84-year-old woman was admitted with a 24-h history of colicky abdominal pain, increasing abdominal distension and constipation. The woman was a known arteriopath and had a history of abdominal pain after eating. She was in atrial fibrillation. The abdomen was distended, mostly on the right side where there was localized tenderness. Bowel sounds were active but not obstructive in character. There were no signs of peritonitis, and rectal examination and sigmoidoscopy findings were normal. Plain radiographs showed gaseous distension of the ascending and transverse colon, and little air in the descending colon. There was no small bowel distension and a provisional diagnosis of closed-loop colonic obstruction was made. A barium enema showed no obstructing lesion, however, and the diagnosis was changed to that of colonic pseudo-obstruction. At 18 h after admission the patient developed signs of right iliac fossa peritonitis and underwent laparotomy.

Operation revealed a gangrenous thin-walled appendix with no adhesion to surrounding structures. The caecum and the ascending and transverse colon were distended and cyanosed, but the descending colon was normal. There was no sharp border between abnormal and normal large bowel. Arterial pulsations were palpable in the ileocolic and middle colic arteries. The caecum and colon were judged to be viable, and routine appendicectomy was performed. The patient made an uncomplicated recovery and was discharged home.

Histological examination demonstrated mucosal and transmur appendicular infarction with acute inflammatory cells infiltrating th wall and adjacent fat. A feeding artery was seen to contain intralumina thrombus. The changes were considered to be those of appendicula infarction caused by thrombosis or thromboembolism of th appendicular artery, although it was not possible to exclude thrombosi secondary to acute appendicitis.

Discussion

The term 'intestinal pseudo-obstruction' was first used b Dudley *et al.*[1] in 1958. Common causes include major traum ischaemia, orthopaedic surgery, retroperitoneal tumour, sepsi myocardial infarction, electrolyte imbalances and uraemia. Th colon is most commonly affected, although the small bowel i not excluded[2]. The aetiology is unknown, but the condition i assumed to be caused by abnormal intestinal motility. Th clinical presentation is similar to that of mechanical coloni obstruction, hence the use of contrast studies. Treatment i directed at the underlying cause and at decompression of th distended bowel, usually endoscopically. The present cas demonstrates that laparotomy is sometimes indicated i patients with radiological features of pseudo-obstruction, eithe to relieve caecal distension and avert rupture, or to treat othe serious intraperitoneal pathology. Such patients should b observed closely and laparotomy should be considered localizing signs or peritonitis develop.

Although necrotizing arteritis of the appendix has bee described[3], no other report of appendicular infarction resultin in colonic pseudo-obstruction has been found. This associatio should be borne in mind in elderly patients with arteriopathy.

Acknowledgements

The authors are grateful to Mr M. J. S. Wilkinson for permission t present this case.

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Short note

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Return to work after inguinal hernia repair

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Repair of inguinal hernia is one of the most common operations performed on men; convalescence time away from work after such surgery constitutes an important loss of income to both individual and nation[1]. It is now generally accepted[1–5] that the patient should return to work within 4 weeks of an uncomplicated inguinal hernia repair. Regardless of occupation, this 'early' return is not associated with an increase in recurrence rate[6], and no discrimination should be made for those in physically demanding employment. Despite this, the authors suspected that patients still remain off work for periods much longer than 4 weeks, largely on the advice of their general practitioners (GPs). This is a report of a retrospective postal survey, investigating when patients return to work after hernia repair and some of the factors influencing this.

Patients and methods

A postal questionnaire was sent to men aged 18–65 years who had undergone unilateral inguinal hernia repair performed as a first-time procedure by a single consultant surgeon (A.N.F.) from January 1982 to December 1991. The operation was performed by the consultant in person, using an overlapping repair of the transversalis fascia for direct hernia and herniotomy with repair of the deep inguinal ring for indirect hernia. The questionnaire asked:

1. Before coming to hospital, how long did you initially expect to need off work?
2. Who gave you this impression?
3. After your hernia repair, how long did you stay off work?
4. Did you think you were off work for an appropriate length of time?
5. Could you have gone back earlier: (a) to a lighter job? or (b) to your own job?
6. Who decided you could return to work?

Patients were also asked to classify their work as light, moderate or heavy, to indicate whether it was manual, sedentary or mixed, to describe their work briefly and to give an indication of the heaviest object they may have had to lift. The definition of light, moderate or heavy work used was based on the patient's own classification and tandardized using other information provided.

Results

A total of 420 questionnaires were sent to patients, 292 of which were returned, a response rate of 70 per cent. Seventy-one of hese were invalid for various reasons including unemployment and early retirement. Of the 221 remaining patients, 76 34 per cent) described their work as light, 85 (38 per cent) as moderate and 60 (27 per cent) as heavy. The intervals from operation to return to work are shown in *Figure 1*.

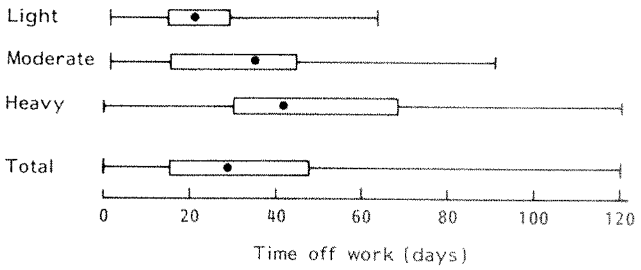

Figure 1 *Time off work according to type of occupation. Values are median (box, interquartile range; bars, range)*

In all, 194 patients (88 per cent) had a preoperative expectation of convalescence time. This expected time correlated well with the time actually taken ($r_S = 0{\cdot}63$, $P < 0{\cdot}0001$). In 131 patients (68 per cent) the expected time was based on information from colleagues, in 54 (28 per cent) from the referring GP and in nine (5 per cent) from the surgeon. Forty patients performing heavy work (73 per cent of those giving valid replies) thought they were off too long and could have returned earlier, to lighter work in 32 cases and to their own job in eight. Thirty-one (46 per cent) of the light workers thought they could have returned sooner. Only 31 (14 per cent) of all patients thought they had returned to work too early and the majority of these were self-employed.

The main influence in the decision to return to work varied with occupation. In men doing heavy work the GP made the decision most frequently (24 cases; 41 per cent) whereas in those performing light work it was more often made without consultation (40 cases; 56 per cent). The early and late returners were also advised from different sources. Of 55 patients who returned within 16 days (first quartile), 38 (69 per cent) made the decision themselves and only seven (13 per cent) were returned 'early' by their GP. However, in the fourth quartile (return to work after 47 days) 34 patients (62 per cent) stated that the GP was the main influence in this delayed return.

Discussion

There have been few recent studies of convalescence after herniorrhaphy. Two surveys in 1981 and 1980 gave mean times of 65 and 51 days respectively[2,5]. The overall median time of 28 days for patients in the present study is considerably lower than both these and suggests there has been a marked trend towards earlier return to work as advocated by a number of authors[1,2,4] following studies carried out in the 1970s.

The misconception that those with physically demanding jobs need longer off work persists. In this study the median time off for men in heavy work was 42 (interquartile range 30–68) days, with 75 per cent being off work for >4 weeks. Almost three-quarters of this group thought they could have returned to some form of work earlier. Men performing heavy work represent roughly one-third of the workforce and there is considerable financial and psychological benefit, both to the individual and in general, in their early return to employment.

The GP was seen as the most important factor in this delayed return to work by both the group performing heavy work and those who returned to work latest. Actual time off work correlated strongly with the preconceived time, and so education at the preoperative stage, initially by the referring GP and reinforced by the surgical team, may be effective.

In conclusion, this study indicates that the time off work following routine inguinal hernia repair is reducing and coming into line with current surgical thinking. However, spurious factors such as the type of work continue to influence this time interval. Education of GPs and, before operation, of patients may be one of method of successfully influencing this.

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Surgical workshop

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Method of separating the peritoneal sac from the spermatic vessels during laparoscopic repair of inguinal hernia

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A popular method of repairing inguinal hernia laparoscopically involves insertion of a piece of polypropylene mesh in the preperitoneal space so that it covers the internal ring, Hesselbach's triangle and the femoral canal. To insert this mesh, it is necessary to separate the peritoneum from the underlying structures. This manoeuvre is particularly difficult over the testicular vessels and vas, which are closely applied to the peritoneum, as is the inferior epigastric artery. A technique is described that makes this part of the operation easy, quick and safe.

Surgical technique

A 19-G needle swaged to a plastic tube is inserted through a small stab wound in the lateral part of the abdomen on the same side as the hernia. To date such a needle has been created by removing the wings from a 'butterfly' needle. The far end of the tubing is attached to a 20-ml syringe containing normal saline and a dilute solution of bupivacaine (0·25 per cent). The needle is visualized with the laparoscope as it enters the peritoneal cavity and picked up using fine graspers. It is then steered towards the spermatic cord and delicately inserted just beneath the peritoneum alongside the spermatic vessels. This enables the tip of the needle to be clearly seen as it advances under the peritoneum (*Figure 1*). When the needle is seen to be in a satisfactory position, the assistant insufflates the saline solution, raising a 'blister' of fluid which separates the peritoneum from the underlying vessels. After satisfactory separation has been achieved, the syringe is filled with either air or carbon dioxide from the pneumoperitoneum. Pressure is then reapplied and air enters the retroperitoneal blister. This event completes the dissection and separates the peritoneum from the underlying vessels by an air pocket. Further similar separation is achieved down the hernia sac and around the inferior epigastric vessels. The peritoneum is then incised cranially and a flap is raised down towards the inguinal ligament. As the air pocket is entered, it is seen that dissection over the vessels is complete.

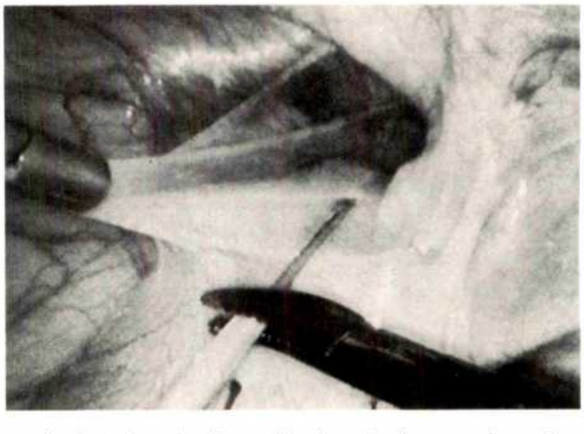

Figure 1 *Injection of saline and bupivacaine between the peritoneum and spermatic vessels, using a modified 'butterfly' needle. Injection of air or carbon dioxide into the blister completes the separation of the sac and vessels*

Discussion

It was previously found that separation of the peritoneum from the spermatic vessels took a great deal of time and had to be performed very carefully because of the danger of incising these vessels and causing bleeding and haematoma formation. Attempts to perform hydrodissection from a needle inserted externally proved difficult and inaccurate. Internal hydrodissection and pneumodissection are now carried out as a first manoeuvre as soon as pneumoperitoneum has been established and the cannulas inserted. The previously difficult dissection is now completed within 1–2 min. This technique has allowed a reduction in the mean operating time for laparoscopic inguinal hernia repair from 70 to 58 min and is strongly recommended for general adoption. Care must be taken to ensure that the needle is not inserted into a blood vessel, but this can be avoided as the manoeuvre is carried out under direct vision with laparoscopic magnification. The injection of fluid alone results in oedema and does not give rise to a clear dissection plane. The secondary injection of air or carbon dioxide overcomes this problem. A special needle with attached tubing is being developed to allow easier insertion into the peritoneal cavity than is possible with the modified butterfly needle.

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Emergency liver resection for spontaneous rupture of hepatocellular carcinoma complicating cirrhosis

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From 1983 to 1991, 42 patients were operated on for hepatocellular carcinoma (HCC) complicating cirrhosis. Five presented with spontaneous rupture of the tumour: three had posthepatitis B and two non-A non-B cirrhosis. By contrast, 65 per cent of patients with non-ruptured HCC had alcoholic cirrhosis ($P < 0{\cdot}01$). Laparotomy was carried out on an emergency basis (four patients) or after a 12-h delay (one) because of haemodynamic instability. Liver resection was performed in four cases (two wedge resections, one segmentectomy III, one extended right hepatectomy) and in the fifth patient hepatic artery ligation was performed. Bleeding was controlled after all four resections with one postoperative death, while the patient treated by ligation died during operation. Of the three surviving patients after liver resection, two died, 6 and 12 months after surgery. One patient is alive with recurrent tumour 43 months after extended right hepatectomy. The present data, combined with analysis of 250 cases of ruptured HCC from the literature, indicate that emergency resection is the treatment of choice in patients with limited tumour and preserved liver function. Transcatheter hepatic artery embolization, if available, is the next choice for high-risk patients or before surgical resection of the tumour. More conservative surgical approaches are the last choice because of poor reported results.

Spontaneous tumour rupture is a dangerous complication of hepatocellular carcinoma (HCC). It is uncommon in Western countries and most reports in the literature have come from the Far East[1–10]. Intraperitoneal bleeding and underlying chronic liver disease explain the high mortality rate of 50–85 per cent[3,4,9,10]. Recommended treatments include hepatic artery ligation[4,9] and, more recently, transcatheter hepatic artery embolization[5,6,8,10]. By contrast, emergency liver resection has rarely been advocated[1,7].

The present paper reports experience of the management of ruptured HCC complicating cirrhosis in five patients, four of whom underwent emergency hepatectomy.

Patients and methods

From May 1983 to September 1991, 48 patients with HCC underwent operation; 42 had liver cirrhosis. The aetiology of cirrhosis was alcohol abuse (24 patients), chronic hepatitis B virus infection (ten), chronic hepatitis non-A non-B virus infection (five) and unknown (three).

Of the 42 patients, five were admitted as an emergency with acute haemoperitoneum from spontaneous rupture of HCC and are the subject of the present paper.

Location of liver tumour was defined according to the segmental anatomy[11]. Severity of liver failure was assessed using the Child–Pugh classification[12].

Results

Clinical features

Details of the five patients are given in *Table 1*. The mean age was 54·6 (range 44–68) years. All patients had non-alcoholic liver cirrhosis that followed hepatitis B (three patients) or hepatitis non-A non-B (two). By contrast, 24 of 37 patients (65 per cent) with non-ruptured HCC had alcoholic cirrhosis

Table 1 *Details of five patients operated on for spontaneous rupture of hepatocellular carcinoma*

Patient no.	Age (years)	Sex	Aetiology of cirrhosis	Child–Pugh grade	Tumour size (cm)	Tumour location (segment)	Peroperative blood transfusion (units)	Operative procedure	Outcome
1	51	M	Hepatitis B	A	4	IV	6	Tumour excision	Died at 6 months from liver failure
2	44	M	Hepatitis B	B	15	II–V	7	Hepatic artery ligation	Peroperative death
3	45	M	Hepatitis B	A	10	III	10	Segmentectomy	Died at 12 months from liver failure
4	68	F	Non-A non-B hepatitis	B	5	III	5	Tumour excision	Died at 10 days from liver failure
5	64	M	Non-A non-B hepatitis	A	7	IV, V, VIII	10	Extended right hepatectomy	Alive at 43 months with recurrence

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(Yates' $\chi^2 = 7{\cdot}5$, 1 d.f., $P < 0{\cdot}01$). Cirrhosis had been diagnosed previously in three patients and another was known to have a liver tumour before the acute presentation. Two patients had right upper quadrant pain during the week preceding the acute presentation. On admission, all patients had abdominal pain and tenderness and were hypotensive.

The diagnosis of tumour rupture was suspected before operation in four patients with spontaneous haemoperitoneum; this group included three patients with known liver cirrhosis and one patient with a known liver tumour. In these four, diagnosis of haemoperitoneum was confirmed by paracentesis (two cases) or emergency ultrasonography (two). Emergency laparotomy was performed in these four patients because of haemodynamic instability. The fifth patient was taking oral anticoagulants for aortic valve replacement; abdominal ultrasonography showed free intra-abdominal fluid. After 12 h of observation, laparotomy was undertaken because of persistent haemodynamic instability despite blood transfusion.

Operative findings

A right subcostal incision was used for the four patients in whom diagnosis was established before operation. In the fifth patient, an upper midline incision was used. The mean(s.d.) volume of haemoperitoneum was 3·4(1·1) (range 3–5) litres. All patients had liver cirrhosis confirmed by pathological examination. The tumour was located in the left lobe in three cases, in the right lobe in one and centrally in one. The mean(s.d.) tumour size was 8·2(2·2) (range 4–15) cm. Peroperative packed red blood cell transfusion ranged from 5 to 10 units.

Liver resection was performed in four cases: two wedge resections, one segmentectomy III and one extended right hepatectomy (segments IV–VIII). Hepatic inflow occlusion (Pringle manoeuvre) was used in all but one case where elective clamping of the right portal pedicle was performed for extended right hepatectomy. One patient had an irresectable bulky central tumour and hepatic artery ligation was performed.

Outcome

Control of bleeding was obtained in all four patients in whom tumour resection was performed. Where hepatic artery ligation was undertaken, haemostasis was not achieved and the patient died during operation. One patient died from liver failure 10 days after hepatectomy. This gave an operative mortality rate of 25 per cent (one of four) after liver resection and 40 per cent (two of five) in the whole group. Two of the three patients surviving after liver resection died; one at 6 months from liver failure and one at 12 months from recurrent HCC. One patient is alive 43 months after extended right hepatectomy but has developed recurrent tumour in the remaining liver and has been treated by hepatic artery chemoembolization.

Discussion

Prognosis of ruptured HCC is poor and in reported series[1–10] most patients die within 1 month. The present data, although from a limited number of patients, suggest a possible benefit of emergency liver resection since three of four patients survived >6 months, one being alive 43 months after major hepatectomy.

Spontaneous rupture of HCC complicating cirrhosis is uncommon and is observed most often in Far Eastern countries where this complication is a presenting feature in 5–15 per cent of patients hospitalized for HCC[1,3–10]. In the present study spontaneous rupture of HCC complicating cirrhosis accounted for 12 per cent of patients with HCC who underwent surgery. This percentage does not reflect the actual prevalence of spontaneous rupture of HCC in cirrhosis because 75–95 per cent of patients with cirrhosis and HCC are not suitable for surgery, because of liver failure or tumour extension[13]. In the present series spontaneous rupture of HCC occurred in patients with posthepatitic cirrhosis although alcoholism was the most frequent cause of cirrhosis in patients with HCC as a whole. HCC rupture is more frequent in Asia where chronic viral hepatitis is the main cause of cirrhosis[14]. The data suggest that rupture of HCC may be more frequent in patients with non-alcoholic cirrhosis.

In the present series, diagnosis of rupture of HCC was made before operation in four of the five cases. Spontaneous haemoperitoneum in a patient known to have cirrhosis or liver tumour is highly suggestive of tumour rupture. Haemoperitoneum can be confirmed readily by paracentesis. The liver tumour should be assessed by emergency ultrasonography or computed tomography if possible.

Several treatments have been proposed for spontaneous rupture of HCC. A review of the literature, comprising data on 255 patients (including the present ones) with spontaneous HCC rupture[1–10], of whom 246 came from Far Eastern countries[1,3–10], has been carried out (*Table 2*). Indications for emergency therapy included haemorrhagic shock and/or persistent bleeding, and acute abdomen. The severity of this complication is attested by an overall 1-month survival rate of

Table 2 *Treatment used in 255 reported cases of spontaneous rupture of hepatocellular carcinoma complicating cirrhosis*

Reference	Year	No. of patients	Resection	Plication	Hepatic artery ligation	Packing	Exploratory laparotomy	Transcatheter arterial embolization	Non-operative management
Ong and Taw[1]	1972	42	13 (31)	1 (2)	12 (29)	8 (19)	3 (7)	0	5 (12)
Mokka *et al.*[2]*	1976	4	2 (50)	2 (50)‡	1 (25)‡	0	0	0	0
Nagasue and Inokuchi[3]	1979	7	2 (29)	1 (14)	2 (29)	0	1 (14)	0	1 (14)
Chearanai *et al.*[4]	1983	63	1 (2)	3 (5)	26 (41)	6 (10)	1 (2)	0	26 (41)
Nouchi *et al.*[5]	1984	4	0	0	0	0	0	4 (100)	0
Sato *et al.*[6]	1985	6	0	0	0	0	0	6 (100)	0
Chen *et al.*[7]	1988	27	14 (52)	3 (11)	6 (22)	4 (15)	0	3 (11)§	0
Lai *et al.*[9]	1989	60	7 (12)	2 (3)	47 (78)	0	0	0	4 (7)
Dewar *et al.*[10]	1991	37	11 (30)	8 (22)♯	12 (32)♯	2 (5)	1 (3)	4 (11)	2 (5)
Cherqui *et al.**	1993	5	4 (80)	0	1 (20)	0	0	0	0
Total		255	54 (21)	20 (8)	107 (42)	20 (8)	6 (2)	17 (7)	38 (15)
Overall 1-month survival		93 (36)	37 (69)	5 (20)	37 (35)	1 (5)	0	12 (71)	4 (11)
Overall 1-year survival		13 (5)	11 (20)	0	1 (1)	0	0	1 (6)	0

Values in parentheses are percentages. *Western series; ‡one patient had both procedures; §before surgical resection 5–10 days later; ♯three patients had both procedures

36 per cent. Factors associated with poor survival include haemorrhagic shock[10] and advanced cirrhosis (Child–Pugh grade C)[9]. The relationship between survival and type of operative procedure remains unclear. Liver resection was performed in 54 patients and was associated with a 1-month survival rate of 69 per cent. Hepatic artery ligation, the most commonly used haemostatic procedure in the literature, gave a 1-month survival rate of 24 per cent in the largest single reported series of 47 patients[9] and 35 per cent in the total of 107 reported cases. Hepatectomy was probably used in the lowest risk patients, which may account for the better survival after resection.

Some authors have recommended a conservative approach, such as hepatic artery ligation, even in patients with potentially resectable tumours[4,9]. However, the present authors support a more aggressive policy and suggest that liver resection, when feasible, is preferable to hepatic artery ligation, which should be reserved for patients with poor liver function (Child–Pugh grade C), advanced tumour or poor general condition. When performed, selective ligation of the branch supplying the tumour-bearing lobe is as effective as, and may be preferable to, common hepatic artery ligation[9]. Non-operative management has been used in 38 patients because of their extremely poor condition[1,3,9,10] or as a deliberate policy[4]. Four patients survived but the median survival[4] in these was only 1·5 months. A conservative approach seems warranted only in moribund patients.

At the present time, resection for HCC complicating cirrhosis is associated with a 3-year survival rate of 30–40 per cent[15]. After tumour rupture, emergency liver resection may achieve haemostasis and is the only treatment with a reasonable possibility of long-term survival. The 1-year survival rate is 20 per cent (*Table 2*) and 5-year survivors have occasionally been recorded[1,7].

In patients with ruptured HCC, the emergency setting precludes careful evaluation of tumour size and location, and the presence of underlying liver disease. However, preoperative diagnosis of rupture of a liver tumour is often possible and allows preparation for liver surgery with appropriate monitoring, incision and selection of instruments. Resection of bleeding HCC in patients with adequate liver function (Child–Pugh grade A or B) and limited tumours is recommended. Major hepatectomy should be avoided if possible because of the impaired regenerative capacity of the cirrhotic liver[16] and the risk of postoperative liver failure[17]; accordingly, limited resection is preferable[16–18]. However, one of the present patients underwent extended right hepatectomy because of the location and size of the tumour and this patient survived the longest.

Transcatheter arterial embolization is an efficient haemostatic measure with a success rate of 70 per cent[5,6,8]; moreover, it may have therapeutic effect on the tumour, especially when combined with a cytotoxic agent and Lipiodol Ultra Fluid (Guerbet, Aulnay-sous-Bois, France) as chemoembolization, and it can be repeated[19]. Embolization can be followed by semielective liver resection within a few days to avoid recurrent bleeding in low-risk patients[8] and may be the only possible treatment in those at high risk (Child–Pugh grade C, poor general condition, advanced tumour). However, the use of arterial embolization is limited by the emergency presentation of a patient in shock and the immediate need for a trained interventional radiologist.

In conclusion, for spontaneous rupture of HCC complicating cirrhosis, emergency liver resection appears to be the treatment of choice in patients with limited tumour and preserved liver function. Transcatheter hepatic artery embolization, if available in an emergency context, is an option in high-risk patients and may be used as a prelude to resection. More conservative surgical approaches such as hepatic artery ligation, packing and plication should be the last choice because of the poor results.

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Vitamin C status in patients with acute pancreatitis

Vitamin C is a key antioxidant in human blood plasma and hence could influence the outcome of conditions such as acute pancreatitis in which oxidative stress apparently plays a pivotal role. The concentrations of vitamin C and its immediately bioavailable form, ascorbic acid, in fasting plasma samples from 30 healthy volunteers were compared with those in admission samples from 29 consecutive patients with acute pancreatitis and 27 patients with other acute abdominal crises. Median (range) levels of vitamin C and ascorbic acid, respectively, were 15 (6·3–19) and 12 (4·5–18) μg/ml in the control group, 2·8 (0·3–10) and <0·5 (<0·5–6·0) μg/ml in patients with acute pancreatitis, and 3·7 (0·6–15) and 2·3 (<0·5–15) μg/ml in those with other acute abdominal problems. Admission plasma samples showed equally low vitamin C levels in both groups of patients ($P < 0.001$ versus *controls), but those from patients with acute pancreatitis were further characterized by a disproportionate reduction in ascorbic acid, such that the concentration of ascorbic acid and its ratio to vitamin C were both significantly lower than in samples from patients with an acute abdomen* ($P < 0.005$ *and* $P < 0.001$ *respectively). It is concluded that the stress of an acute intra-abdominal crisis is accompanied by a non-specific decrease in the plasma level of vitamin C. In acute pancreatitis early and profound oxidative stress compounds this problem by denaturing the available vitamin. There may be a case for the judicious parenteral administration of ascorbic acid to patients with acute pancreatitis to boost plasma antioxidant defence.*

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Oxidative stress is emerging as the pivotal effector of acinar cell injury in experimental acute pancreatitis, irrespective of the initiating agent or its route of attack[1–3]. If this is also true for acute pancreatitis in humans, then parenteral antioxidants could offer specific first-line therapy. Recent studies have indicated that ascorbic acid, the bioactive form of vitamin C, is a key antioxidant in human blood plasma and has particular activity against the powerful oxidants released by activated leucocytes and macrophages[4]. These phagocytes have been incriminated in the transformation from oedematous to haemorrhagic pancreatitis[1–3]. For these reasons, vitamin C and ascorbic acid levels have been studied in admission plasma samples from patients with acute pancreatitis and from those with miscellaneous causes of an acute abdomen.

Patients and methods

Clinical

Three groups were studied (*Table 1*): (1) 30 non-smoking controls including healthy hospital personnel and patients with minor surgical problems; (2) 29 consecutive patients with acute pancreatitis diagnosed by conventional criteria; and (3) 27 patients presenting with an acute abdomen in whom acute pancreatitis was subsequently considered to be unlikely from blood amylase levels and/or pancreatic ultrasonography. Patients were admitted to one of three hospitals in Greater Manchester (Manchester Royal Infirmary, Tameside General Hospital or Park Hospital, Trafford).

A blood sample was obtained after an overnight fast from control subjects and at admission from patients. Material from patients with acute pancreatitis was obtained over a 12-month period from October 1989; about half the material from healthy and diseased controls was obtained during the same period and the remainder between February and May 1992. Acute pancreatitis was graded mild or severe at admission by a combination of clinical[5] and biochemical[6] criteria. After recording the interval between the first symptom and diagnosis, patients were entered into a multicentre randomized trial of glutathione precursors and the putative cause of pancreatitis noted at a later date (*Table 1*). There was no prospective attempt to score severity of illness in other patients with an acute abdomen. A retrospective assessment was made from hospital records, paying particular regard to age, previous medical illness, essential physiological functions, results of routine blood tests, length of hospital stay and outcome. Follow-up information was sought on patients with an acute abdomen who had

Table 1 *Clinical data*

Clinical group	No. of patients
Non-smoking volunteers ($n = 30$)	
Patients with acute pancreatitis ($n = 29$)	
Admitted <15 h from first symptom	11
Admitted ≥15 h from first symptom	18
Graded mild	24
Graded severe	5
Gallstones	12
Alcohol	4
Drugs	4
Idiopathic	9
Patients with other acute abdominal crises ($n = 27$)	
Empyema of the gallbladder	1
Acute cholecystitis	4
Biliary colic	2
Chronic cholecystitis	2
Perforated duodenal ulcer	2
Diverticulitis	2
Appendicitis	4
Colonic obstruction (cancer)	2
Small intestinal obstruction (Crohn's disease)	2
Non-specific	6

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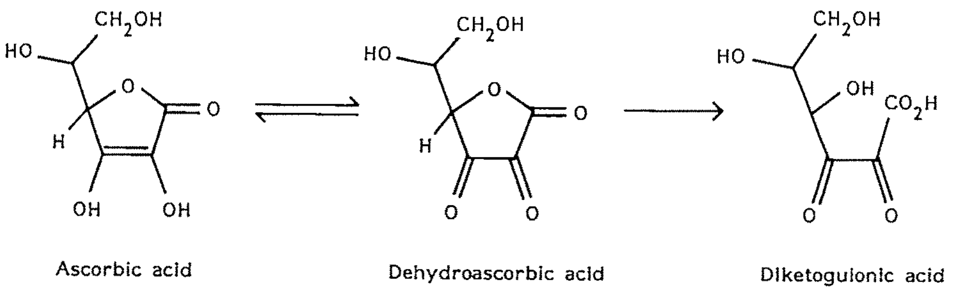

Figure 1 *Components of vitamin C. The irreversibly denatured product 2,3-diketo-1-gulonic acid disintegrates into oxalic acid and* L*-threonic acid*

been studied 12–18 months earlier. As oral antioxidant supplements are routinely given to patients at Manchester Royal Infirmary after an attack of pancreatitis until blood levels are normalized, follow-up blood samples from untreated patients were obtained whenever possible from the other two participating centres. Follow-up samples were obtained at 2, 7 and 14 days while the patients remained in hospital.

Biochemical

Blood samples were collected into heparinized tubes and immediately centrifuged to separate plasma. An aliquot was taken into an equal volume of 10 per cent ice-cold trichloroacetic acid to measure the level of vitamin C, which includes ascorbic acid and its metabolites (*Figure 1*). A second aliquot was diluted with an equal volume of 10 per cent metaphosphoric acid for the specific measurement of ascorbic acid. After centrifugation the supernatants were frozen at −70°C. The vitamin C level was measured by a spectrophotometric method[7] that involves derivatization with 2,4-dinitrophenylhydrazine after the copper-catalysed oxidation of ascorbic acid to its reversibly oxidized product dehydroascorbic acid (DHAA) and the irreversibly denatured form diketogulonic acid (*Figure 1*). Recovery of the vitamin from samples 'spiked' with ascorbic acid was 102–107 per cent; within-batch and between-batch coefficients of variation were 3·4 and 6·0 per cent respectively and the lower limit of detection 0·3 µg/ml. Ascorbic acid concentration was measured by high-pressure liquid chromatography (HPLC) as described previously[8] using an Apex amino column (5 µm, 250 × 4·6 mm; Jones Chromatography, Hengoed, UK) and a Copell ODS precolumn (40 µm, 50 × 4·6 mm; Technicol, Stockport, UK). Recovery of ascorbic acid from 'spiked' samples averaged 98 per cent; within-batch and between-batch coefficients of variation were 4·7 and 6·8 per cent respectively and the lower limit of detection 0·5 µg/ml. The reversibly oxidized product DHAA was sought by analysing 400-µl aliquots after incubation for 15 min with a solution of the strong reducing agent homocysteine (200 µl of 1 per cent solution in 45 per cent potassium phosphate). Any increase in ascorbic acid recorded reflects the amount of DHAA in the original sample. In theory, the quantity of diketogulonic acid can be gauged from the difference in colorimetric values for total vitamin C and the sum of ascorbic acid and DHAA values obtained by HPLC.

Statistical analysis

Relationships between vitamin C and ascorbic acid levels were investigated by parametric methods (Student's *t* test, paired *t* test, Kendall's correlation coefficient). Ascorbic acid concentrations <0·5 µg/ml were regarded as zero when the percentage of vitamin C as ascorbic acid was calculated. Non-parametric methods were used for intergroup comparisons (χ^2 analysis, Wilcoxon matched pairs signed rank test, Kruskal–Wallis one-way analysis of variance, Mann–Whitney *U* test). Differences were considered to be significant when $2P < 0·05$.

Results

There were significant overall differences in plasma concentrations of vitamin C and ascorbic acid in the three groups ($P < 0·001$, Kruskal–Wallis test).

Control subjects

Reference ranges were derived by analysis of all 30 samples for vitamin C and 26 for ascorbic acid; four samples that showed interference in the HPLC trace were excluded. Values for plasma ascorbic acid (median 12 (range 4·5–18) µg/ml) were significantly lower ($P = 0·02$) than for vitamin C (median 15 (range 6·3–19) µg/ml), yielding a median ratio of ascorbic acid to total vitamin C of 87 (range 66–117) per cent. This shortfall could not be attributed to DHAA.

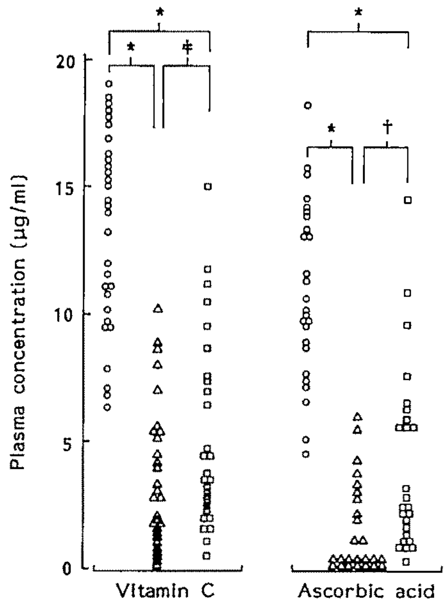

Figure 2 *Vitamin C and ascorbic acid concentrations in plasma from healthy controls* (○), *patients with acute pancreatitis* (△) *and patients with other causes of an acute abdomen* (□). *P < *0·001*; †P < *0·005*; ‡P *not significant* (χ^2 *and Mann–Whitney* U *tests*)

Patients with pancreatitis

Compared with control subjects, patients with acute pancreatitis had significantly reduced levels of vitamin C (median 2·8 (range 0·3–10) µg/ml) and ascorbic acid (median <0·5 (range <0·5–6·0) µg/ml). The concentration of vitamin C in plasma was below the lowest control value in 24 of 29 patients (83 per cent) (*Figure 2*). The proportion of patients with vitamin C below the lower limit of the reference range in various subgroups was: presentation within 15 h of the first symptom, 91 per cent (ten of 11 patients); presentation after 15 h, 78 per cent (14 of 18); mild disease, 79 per cent (19 of 24); and severe disease, 100 per cent (five of five). The distribution of vitamin C concentrations was not different for various aetiological factors (Kruskal–Wallis test), median (range) values being: gallstones, 2·9 (0·1–8·7) µg/ml; alcohol, 1·4 (0·6–3·3) µg/ml; drugs, 4·5 (0·5–8·9) µg/ml; and idiopathic, 4·0 (1·6–10·3) µg/ml.

Ascorbic acid could not be measured because of interference in the HPLC trace of four samples. Of the remaining 25 samples, 23 (92 per cent) had an ascorbic acid level below the lowest control value. There were 14 samples (56 per cent) without detectable ascorbic acid, i.e. <0·5 µg/ml, including eight of ten from patients with gallstone pancreatitis, three of four from those with an alcoholic cause, one of two valid samples from patients with drug-induced disease and one of seven valid samples from those with an idiopathic aetiology. As in control samples, there was a shortfall in plasma ascorbic acid relative to vitamin C concentration (*Figure 2*) but the difference was more striking ($P < 0{\cdot}001$) and the median ratio of ascorbic acid to total vitamin C was 0 (range 0–97) per cent ($P < 0{\cdot}001$ *versus* controls). DHAA was detected in plasma of only two patients with pancreatitis graded as mild (0·8 and 2·5 μg/ml). The range of ascorbic acid values and ratio of ascorbic acid to total vitamin C were similar in patients with mild and severe disease.

Patients with an acute abdomen

Patients with an acute abdomen showed significant reductions compared with control subjects in plasma levels of vitamin C (median 3·7 (range 0·6–15) μg/ml) and ascorbic acid (median 2·3 (range <0·5–15) μg/ml). Three patients were regarded as being gravely ill by the surgical teams at admission: one patient aged 83 years with acute diverticulitis and *Klebsiella* septicaemia; one diabetic patient aged 32 years with empyema of the gallbladder; and one patient aged 57 years with long-standing epilepsy and obstructive airway disease with acute abdominal pain of uncertain origin. Admission plasma samples from the group as a whole had vitamin C levels as low as those from patients with acute pancreatitis (*Figure 2*). Seventeen patients (63 per cent) had lower values than the lowest control level, including all seven with acute biliary problems, two with diverticulitis, two with colonic cancer, two with Crohn's disease, one of four with appendicitis, one of two with duodenal ulcer, one patient with bronchitis and one with unexplained abdominal pain.

The plasma ascorbic acid level was below the detection limit in only one of 25 patients compared with 14 of 25 in the group with acute pancreatitis (4 *versus* 56 per cent, $P < 0{\cdot}001$). Excluding two samples (from patients with acute cholecystitis and diverticulitis with *Klebsiella*) where there was interference in the ascorbic acid assay, the normal relationship between vitamin C and ascorbic acid was preserved overall: plasma ascorbic acid levels in patients with an acute abdomen were significantly higher than in those with acute pancreatitis ($P < 0{\cdot}005$) and the ratio of ascorbic acid to vitamin C (median 77 (range 0–106) per cent) generally conformed with that in controls and was significantly higher than for patients with pancreatitis. There were ten cases, however, where the ratio of ascorbic acid to vitamin C was lower than the lowest control value, including six other patients with acute biliary problems, a second patient with acute diverticulitis, one patient with colonic cancer and two with pain of unknown origin.

No correlation was seen between admission blood leucocyte count, temperature or time spent in hospital on the one hand and values of vitamin C, ascorbic acid or percentage of vitamin C as ascorbic acid on the other.

Regression analysis

A significant linear relationship was found between plasma vitamin C and ascorbic acid concentrations in the control group (ascorbic acid = 0·77 × vitamin C + 0·40; $P < 0{\cdot}001$) and in patients with an acute abdomen, excluding the patient with acute cholecystitis, in whom the ascorbic acid level was below the detection limit (ascorbic acid = 1·05 × vitamin C − 2·26; $P < 0{\cdot}001$). The slopes (mean(s.d.) 0·77(0·09) and 1·05(0·14) respectively) and intercepts (mean(s.d.) 0·40(1·19) and −2·26(1·25) respectively) of the two equations did not differ significantly and in each the intercept was not significantly different from zero. A similar analysis was not possible for the group of patients with acute pancreatitis because precise concentrations for ascorbic acid could not be determined in 50 per cent of cases where levels were below the assay detection limit.

Discussion

The metabolism of vitamin C is complex, differing markedly with dose and species, and defies easy quantitation. Humans, non-human primates and guinea-pigs cannot synthesize th vitamin and rely on dietary intake to meet tissue requirement There is no easy measure of that requirement and it is doubtfu whether the recommended dietary allowance of 45 μg/day fo humans is adequate[9]. Dietary vitamin C is absorbed in th bioactive form of ascorbic acid through an active transpo system that is saturated[10] when the daily dose of ascorbic acid exceeds 1 g. Renal excretion is the major route of disposal Healthy adult men have an average body pool of 1·5 g ascorbi acid. Although plasma contains only 2·5 per cent of this poo vitamin C metabolism is usually described in terms of plasma concentrations because plasma contains the highest proportio of the vitamin among the blood fractions[11] and because ther are clear relationships between vitamin C intake and plasm levels in healthy subjects, during experimental vitamin C deficiency and after vitamin C supplementation[11,12].

A single biochemical method for quantitation of the various forms of vitamin C (*Figure 1*) has remained elusive. The combination of a spectrophotometric method that gives a globa measure of the three major metabolites which constitute vitami C, and a two-step HPLC system that measures ascorbic aci initially and then ascorbic acid plus DHAA after treatment o the sample with a strong reducing agent, is the only availabl option. This approach is time consuming, but has been used to demonstrate oxidative stress (by a fall in the ratio of ascorbic acid to its oxidized metabolites) in patients with rheumatoid arthritis[13]. The present study was prompted by several linked observations relating to acute pancreatitis. Oxidative stres appears to be the initiator of acinar cell injury in experimental pancreatitis, and frustrated phagocytosis, which leads to th wholesale extracellular discharge of oxidants along with active proteases and other powerful chemicals, may be involved in the transformation of oedematous mild pancreatitis to haemorrhagic lethal disease with multisystem failure[1–3]. A similar evolution in human pancreatitis has been suggested by recent reports[1–3,14–16]. Ascorbate is increasingly being recognized as the most important antioxidant in human blood plasma; it has particular efficacy against hypochlorous acid which is released extracellularly when phagocytosis i excessive[4]. Ascorbic acid is also a key antioxidant within cell where it helps to recycle vitamin E and thus, indirectly, to refurbish reduced glutathione after its oxidation[17].

Analysis of fasting plasma samples from healthy controls showed a significant shortfall in ascorbic acid relative to vitamin C concentrations, and reanalysis after treatment with a strong reducing agent did not correct the deficit. The implication is that the inert metabolite diketogulonic acid accounts for the difference, but the fraction is too low to make any biological impact on the overall vitamin C-related reducing capacity of plasma.

Studies in experimental models of pancreatitis indicate that pancreatitic oxidative stress occurs within the first 30 min of induction[2,3]. Since an average of 10 h elapses between onset of pain and the diagnosis of human acute pancreatitis, a reduction in the ratio of ascorbic acid to vitamin C in admission blood samples was anticipated because of oxidative stress, but not the very low levels of total vitamin C observed; such low levels are traditionally associated with inadequate premorbid intake and low tissue reserves of the vitamin[18]. The outcome of home inventory studies of diet in patients with recurrent acute pancreatitis (who had not altered their diets during attacks)[19–21] suggests that past diet may explain this result. This would also explain why plasma vitamin C levels had not normalized within 2 weeks of the attack (*Figure 3*). The median concentration of vitamin C in plasma was of the order associated with scurvy although none of the patients in the present study had this condition. Vitamin C deficiency and scurvy have not been linked with acute pancreatitis previously, implying that factors in addition to poor diet contributed to the extremely low levels of vitamin C observed. Possibilities include sequestration of vitamin C from plasma into blood cells, diversion of plasma vitamin C (via interstitial fluid) into the pancreas, and enhanced renal excretion.

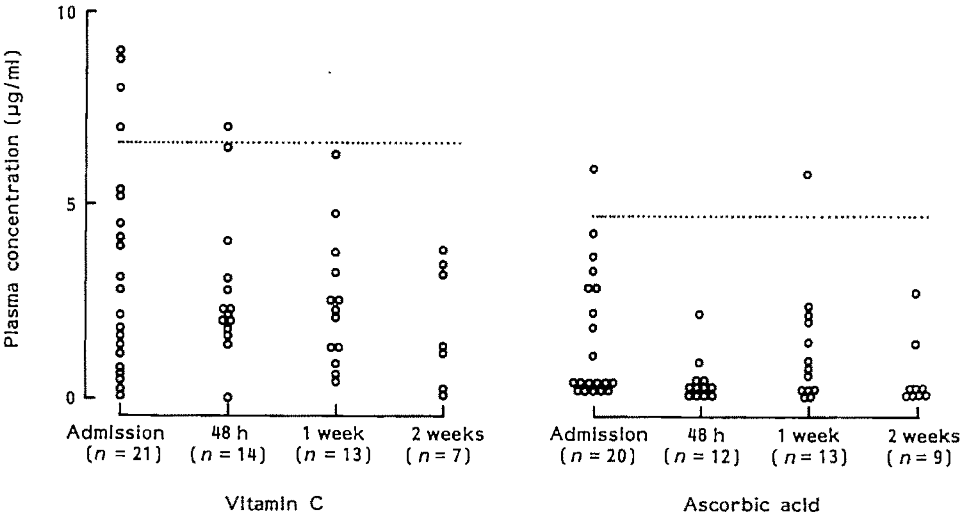

Figure 3 *Follow-up data on vitamin C and ascorbic acid levels in plasma from patients with acute pancreatitis.* ·····, *Lower limit of reference range*

The first of these hypotheses seems improbable because other acute conditions have been shown to decrease, rather than increase, the level of vitamin C in leucocytes in elderly people[22]. That vitamin C may be diverted from plasma into an acutely inflamed organ or that renal clearance of the vitamin may be enhanced under these circumstances are more plausible interpretations. The present study of patients with other causes of an acute abdomen aimed to distinguish these possibilities. The plasma concentration of vitamin C in this heterogeneous group was of the order found in patients with acute pancreatitis, representing a reduction of 70–75 per cent compared with control samples. Since the maximal reported fall after surgical trauma is 30 per cent[23], it seems likely that diversion of the vitamin from plasma into an acutely compromised organ and/or inadequate premorbid dietary intake also contributed to the low plasma vitamin C levels in this group. Proof of these interpretations must await experimental studies, and follow-up plasma and dietary vitamin C assessments respectively. However, the very low plasma vitamin C levels of two of the present patients with colonic cancer (2·0 and 3·1 µg/ml) are noteworthy, because they concur with reports of low premorbid antioxidant status in patients with a variety of malignancies[24].

A disproportionate decrease of plasma ascorbic acid compared with the prevailing level of vitamin C was a feature of acute pancreatitis in the present study. The implication of oxidative stress is independently supported by the observation that the same serum samples contained significantly higher concentrations of a marker of free radical attack on lipids than those from controls[25]. Profound oxidative stress in the vascular compartment thus prevails by the time patients are admitted with acute pancreatitis irrespective of putative aetiology and whether the illness was regarded as mild, as in the majority of patients, or was expected to pursue a severe course. The normal relationship between ascorbic acid and vitamin C was preserved overall in patients with other causes of an acute abdomen, including three who were gravely ill.

The present study indicates the need for detailed exploration of vitamin C metabolism in patients with acute pancreatitis and other acute intra-abdominal crises, including measurement of renal clearance in the acute phase and dietary inventories on full recovery. The results also raise several intriguing questions, not least concerning the biological significance of the low admission plasma levels of vitamin C and ascorbic acid in patients with acute pancreatitis and their possible relevance for treatment. It is difficult to disregard the findings as epiphenomena in view of mounting evidence that oxidative stress underlies experimental acute pancreatitis[1–3]. It is not proposed that vitamin C deficiency causes the disease but rather that it renders the pancreas vulnerable to oxidative stress when the pancreatic oxidant load increases because of transient ductal obstruction, ischaemia–reperfusion injury or other reasons[1–3]. The value of oral antioxidant supplements, including vitamin C, in preventing recurrence of acute or acute-on-chronic pancreatitis has been proven in a placebo-controlled trial[26]. With regard to therapy for a first attack, which is associated with a mortality rate of up to 20 per cent and morbidity in a further 20 per cent, preliminary observations suggest that an intravenous dose of 0·5 g ascorbic acid per day, administered concurrently with a glutathione precursor to combat leucocyte-derived oxidants[3,15,16], is likely to be safe and may be effective in accelerating recovery. A recent study of experimental haemorrhagic pancreatitis strengthens this optimism[27].

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Prospective comparison of C-reactive protein level, Ranson score and contrast-enhanced computed tomography in the prediction of septic complications of acute pancreatitis

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Randomized clinical trials of antibiotic prophylaxis in acute pancreatitis are now warranted in the light of recent evidence of pancreatic penetration of certain antibiotics at therapeutic minimal inhibitory concentrations. The aim of the present prospective clinical study was to investigate whether there are detectable risk factors for pancreatic sepsis in acute pancreatitis that would allow better selection of patients for inclusion in clinical trials. Fifty-nine consecutive patients with acute pancreatitis were recruited and submitted to admission baseline and 48-h determinations of Ranson score, and assay of C-reactive protein at admission and weekly intervals thereafter. Contrast-enhanced computed tomography (CT) was also performed within 24 h of admission. Pancreatic sepsis, defined as infection of pancreatic and/or peripancreatic collections, was demonstrated in all cases by culture of samples obtained by needle aspiration and at laparotomy. Although all prognostic indices correlated significantly with sepsis, multivariate logistic regression analysis showed that the only variables predictive of the risk of subsequent sepsis were the presence and extent of necrosis. Early detection of pancreatic necrosis by CT should be the primary inclusion criterion in future clinical trials of antibiotic prophylaxis in acute pancreatitis.

Septic complications of acute pancreatitis, such as abscess and infected pancreatic and peripancreatic collections, are a major threat and constitute the most important indications for surgery[1–4]. Although sepsis, which is usually a late complication of acute pancreatitis, has proven unamenable to antibiotic prophylaxis[5,6] in the past, recent evidence suggests that a number of antibiotics that are active against the prevailing flora of pancreatic sepsis[7] are secreted into pancreatic juice at therapeutic minimal inhibitory concentrations[8,9]; moreover, certain antibiotics are also capable of reaching therapeutic levels in pancreatic and necrotic tissue[10]. We believe that the value of antibiotic prophylaxis of pancreatic sepsis now needs to be re-examined by specific clinical trials. Apart from a number of problems concerning the design of such trials (such as the risk of inducing resistance), sound criteria are needed for selection of patients at risk of pancreatic sepsis. A prospective trial was therefore conducted to assess whether a number of the more reliable prognostic indices[11–14] may be of value in predicting septic outcome in acute pancreatitis.

Patients and methods

The prospective study was based on 59 consecutive patients observed between June 1988 and December 1990. All had acute pancreatitis and fulfilled the following criteria: no previous pancreatic disease; no signs of sepsis on admission; no previous antibiotic treatment; admission within 48 h of onset of symptoms; availability of contrast-enhanced computed tomography (CT) within 24 h of admission; and no need for early biliary surgery. *Table 1* summarizes the clinical data of the patients; a further 12 were excluded from the study because of clinically demonstrated non-pancreatic infection requiring antibiotic treatment.

All patients underwent standard admission baseline and 48-h determinations of Ranson's criteria[11]. C-reactive protein (CRP) assay was scheduled at admission and at weekly intervals thereafter. CT was scheduled at 10-day intervals, or more frequently if sepsis was suspected.

On the basis of contrast-enhanced CT at admission, pancreatic findings were divided into four groups[13]: (1) no necrosis; (2) necrosis <30 per cent of pancreatic volume; (3) necrosis 30–50 per cent of pancreatic volume; and (4) >50 per cent necrosis.

All patients were treated with standard intensive therapy (analgesics, total parenteral nutrition, nasogastric aspiration, H_2 antagonists, antiproteases) without antibiotics until sepsis developed. Pancreatic sepsis was confirmed by culture of samples obtained whenever sepsis of any origin was suspected by percutaneous needle aspiration guided by ultrasonography or CT. Final outcome (i.e. infection of pancreatic and/or peripancreatic fluid collections) was then compared with admission data. As the study was confined to septic complications of acute pancreatitis, patients with severe (i.e. necrotic) acute pancreatitis were classified into three groups: those without complications; those who developed proven pancreatic sepsis; and those who developed complications (multiorgan failure) but without pancreatic sepsis.

Table 1 *Aetiology and severity in 59 consecutive patients with acute pancreatitis*

	No.
Aetiology	
Biliary	32 (54)
Alcoholic	19 (32)
Other	8 (14)
Severity	
Mild (non-necrotic)	20 (34)
Severe (necrotic)	39 (66)

Values in parentheses are percentages

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Table 2 *Main features of different forms of acute pancreatitis*

	No.	Aetiology			Ranson score*	CRP level (mg/l)*	CT necrosis		
		Biliary	Alcoholic	Other			<30%	30–50%	>50
Oedematous	20	9	8	3	1·7 (1–3)	50 (8–170)	—	—	—
Necrotic uncomplicated	15	10	4	1	3·2 (2–4)	141 (10–240)	9	5	1
Necrotic septic	17	12	2	3	3·9 (2–6)	192 (85–450)	3	4	10
Necrotic non-septic (multiorgan failure)	7	1	5	1	3·4 (3–4)	146 (110–209)	3	3	1

*Values are mean (range). CRP, C-reactive protein; CT, computed tomography

Table 3 *Comparison of indices in the prediction of septic complications*

	CRP level (mg/l)		Ranson score*	CT necrosis	
	>100	>85		None	>30%
False positives	15	17	3	15	7
False negatives	3	0	8	0	3
Specificity (%)	58	53	92	58	81
Sensitivity (%)	82	100	53	100	82
Positive predictive value (%)	48	50	75	53	67
Negative predictive value (%)	88	100	80	100	91
Accuracy (%)	66	68	79	72	81

CRP, C-reactive protein; CT, computed tomography. *Cut-off score 3

Cut-off values for the tests were chosen according to published data[11–14]. Accuracy and other common reliability indices were calculated. Statistical analyses included both univariate (Mann–Whitney U, Kendall's τ C and χ^2) and multivariate (logistic regression) tests.

Results

There were 37 men and 22 women with a mean age of 55 (range 27–91) years. *Table 2* gives the essential findings.

Twenty patients had non-necrotic pancreatitis with a mild clinical course and all recovered without significant complication.

Pancreatic necrosis was present in 39 patients (66 per cent); of these, 17 developed pancreatic sepsis between the second and fourth weeks and were submitted to surgery. In the majority of these cases (12 of 17), a diffuse infection of large peripancreatic collections was found, whereas in the remaining patients it was necessary to drain a pancreatic abscess (two cases), an infected pseudocyst (one) and a pancreatic infected collection (two). In the former 12 patients the technique of retroperitoneal and peritoneal lavage–drainage[2] was used. There were two operative deaths in this group (12 per cent); in both patients pancreatic necrosis was >50 per cent.

In 15 patients with pancreatic necrosis no complication occurred, while the remaining seven, although suffering from severe multiorgan failure, did not develop pancreatic sepsis and were not analysed further.

Table 3 summarizes findings for the predictive values of the various indices at different cut-off levels. Cross-tabulation of septic outcome against age and aetiology for acute pancreatitis revealed no significant correlation. When further univariate analysis was performed, all the indices under study showed significant correlations with pancreatic sepsis.

CRP levels correlated significantly with pancreatic sepsis whatever the cut-off value ($P < 0{\cdot}0002$, Mann–Whitney U test); the distribution was not normal and the median value in patients without sepsis was 82 mg/l, compared with 160 mg/l in those with sepsis. CRP values in these two groups were 145 and 300 mg/l at the 75th percentile, respectively, and 31 and 130 mg/l at the 25th percentile. Ranson scores correlated with sepsis regardless of the cut-off value (Kendall's τ C $= 0{\cdot}73$, $P < 0{\cdot}0001$); with a cut-off score of 3 the Yates' χ^2 value wa 10·0, with $P < 0{\cdot}002$ (1 d.f.). CT evidence of necrosis wa associated with a higher risk of sepsis ($\chi^2 = 18{\cdot}3$, 1 d.f $P < 0{\cdot}0001$). The extent of necrosis also predicted the risk c sepsis ($P < 0{\cdot}0001$, Mann–Whitney U test).

In contrast, multivariate logistic regression analysis a applied to CT, CRP and Ranson scores showed that only th extent of necrosis on CT correlated significantly with pancreati sepsis, with a coefficient of risk of 5·32 (95 per cent confidenc interval 2·39–11·80) ($P < 0{\cdot}0005$); taking >30 per cen necrosis as the cut-off value increased the coefficient of risk t 11·7 (95 per cent confidence interval 3·29–41·80) ($P < 0{\cdot}0005$ The predicted probability of pancreatic sepsis thus increase nearly fivefold per necrosis score; the predicted probability o sepsis in patients with >30 per cent pancreatic necrosis wa 11·7 times that of those with necrosis ≤30 per cent.

Discussion

This study was designed to ensure that all patients include were admitted within 48 h of onset of symptoms and that C was performed within 24 h of admission, thus allowing bot diagnosis and evaluation of early signs. The data may b discussed both as general observations on the severity of acut pancreatitis and as answers to the specific question posed i the study.

Certain well known features of acute pancreatitis are clearl confirmed, in particular that oedematous pancreatitis neve evolves to complicated acute pancreatitis and that pancreati necrosis is the hallmark of severity, i.e. is essential for th development of pancreatic sepsis and/or multiorgan failure Arguably more interesting is the demonstration of the value o early CT: in this series necrosis was invariably detected withi 72 h of onset of acute pancreatitis, while no patient wit oedematous pancreatitis showed necrotic degeneration beyon that time.

Table 2 shows the low accuracy of Ranson's early predictiv signs and the excessively wide range of CRP values, with hig levels recorded in many patients with oedematous acut pancreatitis or uncomplicated pancreatic necrosis.

Statistical analysis showed that both Ranson score and CR concentration correlated significantly with pancreatic sepsi (*Table 3*). Once again, these findings confirm earlier work an can be explained by the previously described association o CRP with pancreatic necrosis and of Ranson score wit severity[11,12].

Contrast-enhanced CT proved to be the best index in th prediction of septic outcome of acute pancreatitis. This ma have resulted simply from its accuracy in detecting pancreati necrosis[13].

Several reports dealing with the prognostic value of CT ar difficult to evaluate for a number of reasons[13,15–19]. First, th endpoint usually embraces too broad a field (all complications or mortality plus complications). Second, the timing of CT i vague, as it is calculated as starting from the time of admissio and not from the time of onset of pancreatitis and, in som cases[13,15], patients had their first CT scan after 7 or more day in hospital. Finally, CT risk factors vary widely from the extent of pancreatic and peripancreatic 'phlegmons'[15], to CT-detected lesions associated with clinical risk factors[17], to complex systems such as the pancreatic size index[18]. The recent work of Balthazar *et al.*[13], from which the definition and classification of pancreatic necrosis was taken, is different from the present study in its design, since it refers both to early (2–7 days after admission) and late follow-up CT; they calculated the risk of mortality and morbidity on the basis of a compound CT severity index (including peripancreatic inflammation, phlegmons and pancreatic necrosis) and considered the necrosis-related risk of sepsis as more marginal. The most interesting aspect of the present results is the significant correlation between a single simple index (extent of pancreatic necrosis on early CT) and the risk of pancreatic sepsis.

In designing clinical trials of antibiotic prophylaxis of pancreatic sepsis from acute pancreatitis, one should include all patients suffering from necrosis as defined by CT appearances, irrespective of the extent of necrosis.

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Stapling technique for annular pancreas

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The operative technique in an adult patient with an obstructing annular pancreas that was divided using a stapling device is described. This is believed to be the first description of this form of treatment.

Surgical technique

A 61-year-old man presented with a long history of vomiting, weight loss and postprandial epigastric pain. A barium meal showed dilatation of the first and second parts of the duodenum; the third and fourth parts were normal. Radiological appearances were consistent with compression of the duodenum by the superior mesenteric vessels. Upper gastrointestinal endoscopy confirmed a narrowing of the second part of the duodenum with proximal dilatation. Combined selective arteriography and a Gastrografin (Schering Health Care, Burgess Hill, UK) meal demonstrated an abnormal coeliac axis (*Figure 1*). At laparotomy the cause of the duodenal obstruction was found to be an annular pancreas (*Figure 2*). The anterior part of the annular constriction was divided using a GIA stapling device (Auto Suture, Ascot, UK). The patient made an uneventful recovery and was discharged on day 6 after surgery. The result of a postoperative barium meal was entirely normal.

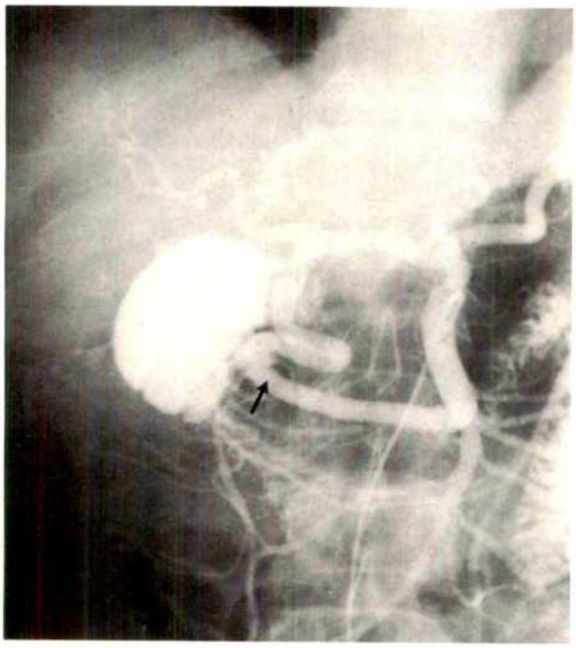

Figure 1 *Combined selective angiography and water-soluble contrast meal demonstrating dilatation of the first and second parts of the duodenum. The superior mesenteric artery has been cannulated. The coeliac axis was stenosed at its origin (not seen here) and an abnormally large collateral vessel is present (arrow)*

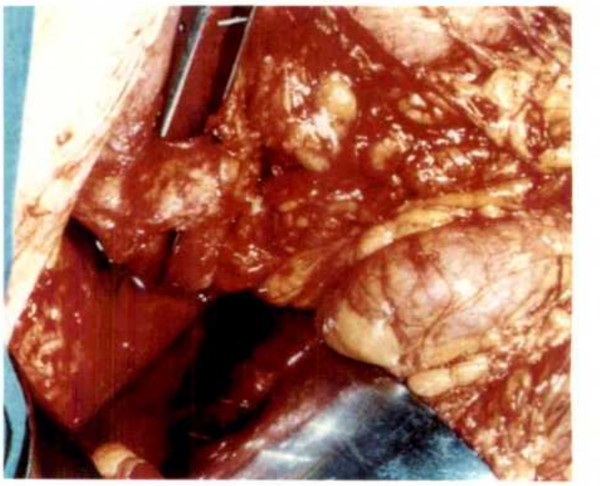

Figure 2 *Non-adherent annular pancreas being lifted away from the duodenum by a forceps*

Discussion

Annular pancreas is an uncommon cause of duodenal obstruction in adults and may be associated with other anomalies[1]. Treatment usually involves some form of bypass[2]. However, the method described here preserves the anatomy of the upper gastrointestinal tract and is technically simple provided that, as in the present case, the annular part of the pancreas is not densely adherent to the duodenum. It was not possible to find the incidence of non-adherence of the annulus in the literature.

Division of the pancreas has previously been associated with high rates of morbidity and mortality[3,4], and this method of treatment has not benefited from recent advances in surgical technique and postoperative care. There have been no recent comparative studies of bypass and division and it is doubtful that bypass is indeed the method of choice for treatment of annular pancreas, particularly in the light of new evidence[5] supporting the successful use of stapling devices in pancreatic surgery.

The technique of stapled division where the annular part of the pancreas is non-adherent and associated duodenal stenosis is absent warrants further evaluation.

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For debate

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Common bile duct stones: a controversy revisited

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Common bile duct (CBD) calculi are known to occur in up to 15 per cent of patients undergoing standard open cholecystectomy[1,2]. Recent surgical practice has been transformed by laparoscopic cholecystectomy, which is associated with a similar complication rate ($\leqslant 5$ per cent), reduced inpatient stay[3], more rapid recovery and an improved cosmetic result compared with the open procedure[4–7]. The problem with the laparoscopic approach is that operative cholangiography is technically more difficult, with reported failure rates, defined as the inability to cannulate or inject the cystic duct, averaging around 25 per cent and ranging from 5 to 75 per cent[5,8,9]. If a high proportion of patients undergo laparoscopic cholecystectomy with inadequate imaging of the CBD, some may later present with retained duct stones and the complications of choledocholithiasis.

There is no consensus on how coexistent duct calculi should be identified and removed in patients with gallbladder stones. Ultrasonography is considered sensitive at detecting gallbladder stones but unreliable for duct calculi, with reported sensitivities ranging from 19 to 55 per cent[10]. A recent review[11] advocated selective use of intraoperative cholangiography with postoperative intravenous cholangiography for technical failures. The criteria used for selection included a history of jaundice, raised serum alkaline phosphatase or bilirubin levels and a CBD diameter >10 mm. For preoperative and postoperative cholangiography the intravenous route was favoured. However, previous studies using intravenous cholangiography reported an appreciable failure rate, difficulties in interpretation, and suboptimal views of the biliary tree[12]. Hypersensitivity reactions, despite modified contrast media, remain a significant problem[13].

Endoscopic retrograde cholangiopancreatography (ERCP), although more invasive, is a sensitive and accurate technique with low morbidity and mortality rates[14,15]. Series have shown that ERCP can be used not only to diagnose duct stones but also to achieve duct clearance in 85–95 per cent of cases in a single procedure[16]. In patients with historical, clinical, biochemical and/or ultrasonographic evidence of choledocholithiasis, duct stones are actually found in 10–60 per cent during ERCP[5,6,17]. In one study[17], a history of jaundice had a sensitivity of 55 per cent and specificity of 42 per cent, and a dilated CBD a sensitivity of 45 per cent and specificity of 24 per cent; no duct stones were found in patients with abnormal liver function test results alone. Use of these criteria for selecting patients for preoperative ERCP before laparoscopic cholecystectomy reduces the risk of duct stones remaining undetected to <2 per cent[5,17,18].

When duct stones are detected before operation, most surgeons favour endoscopic duct clearance for elderly unfit patients[19,20]. Recent reviews[11,21] have advocated surgical CBD exploration and cholecystectomy over ERCP for young (<60 years) fit patients on the grounds that the mortality rate for open exploration in such patients is <1 per cent. Advocates of this policy cite one of the few well matched and randomized trials, which found that preoperative endoscopic sphincterotomy (ES) did not improve the outcome after biliary surgery but, conversely, was associated with higher morbidity and mortality rates than surgery alone[22]. However, this study has been criticized for an unusually high complication rate after sphincterotomy.

Other studies[23–26] have indicated that ES before cholecystectomy is a valid approach and have shown a shorter inpatient stay with preoperative sphincterotomy. There are few long-term studies of the effect of sphincterotomy, but fears that disruption of the choledochoduodenal sphincter may result in an increased incidence of cholangitis and cholecystitis have not been realized[27]. There is, however, evidence that ES enhances complete biliary clearance of pre-existing stones[28].

Some groups[8,11] have recommended routine intraoperative cholangiography, thus avoiding the need for preoperative imaging, even in patients with suspected duct stones. In our view this is irrational. Surely the prime concern in these patients is the identification and clearance of the suspected duct stones. For many patients, particularly the elderly and unfit, ERCP is increasingly recognized as the definitive procedure[19–21]. The risk of further biliary problems after ES appears to be <10 per cent over 3 years; only half of those with such problems have symptoms or complications warranting surgical intervention[29]. If this is true for the elderly and unfit, it may well apply also to the young. In many, ES alone may be sufficient to treat symptoms, without significant risk of recurrence and avoiding surgery.

It would be helpful to be able to identify prospectively the group of patients at greatest risk of developing further biliary problems after sphincterotomy so that pre-emptive cholecystectomy could be offered. One study[30] suggested that patients with cystic duct obstruction, defined by the failure to opacify the gallbladder during ERCP, are at high risk of biliary complications, but this observation has not been regarded as a discriminating factor in many other trials. No specific clinical, biochemical or radiological parameters are regarded as predictive of outcome, although patients presenting with cholangitis are more likely to experience further biliary problems.

For those in whom duct calculi remain undetected until or after laparoscopic cholecystectomy, the best method for stone removal has not been established. Laparoscopic exploration of the CBD is at present confined to certain centres, where success rates for laparoscopic clearance of duct stones have reached over 60 per cent[9]. Nevertheless, the morbidity and mortality rates associated with laparoscopic CBD exploration are unknown, and for most the choice lies between conversion to open exploration or endoscopic removal following cholecystectomy. We favour the latter for stones <2 cm in diameter, with open exploration restricted to patients with larger or impacted stones.

If CBD stones identified at laparoscopic cholecystectomy are left *in situ*, there is a significant risk of acute cholangitis secondary to biliary obstruction. This complication is associated with substantial rates of mortality (>10 per cent) and morbidity. Although numerous studies have advocated emergency endoscopic decompression as first-line treatment, others[21] have suggested that patients may be left in possession of asymptomatic CBD stones without risk.

A policy of preoperative ERCP for selected patients with suspected choledocholithiasis reduces the risk of patients undergoing laparoscopic cholecystectomy with undetected duct stones to <2 per cent[5,17,18]; it concentrates attention on the more significant clinical problem; it offers patients a procedure that, alone, may alleviate symptoms; and it makes subsequent cholecystectomy unnecessary in some.

Routine intraoperative cholangiography may not be required to exclude choledocholithiasis, although many

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surgeons use it to delineate ductal anatomy or identify cystic duct stones that would otherwise remain in the proximal cystic duct stump[31,32]. It has been argued that routine, as opposed to selective, cholangiography reduces the incidence of duct injuries in laparoscopic cholecystectomy[9], but there is no firm evidence to support these anecdotal observations.

Although ERCP is more invasive than some alternatives, it combines diagnosis and potential therapy in a single procedure. With the advent of minimally invasive techniques, such as laparoscopic cholecystectomy, it is appropriate that endoscopic procedures should assume a greater role in the management of choledocholithiasis and cholelithiasis. Minimally invasive surgery has challenged gastroenterologists, radiologists and surgeons[33] to review their approach to the treatment of biliary disease and, one hopes, encouraged them to work more closely together.

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Conventional *versus* laparoscopic surgery for acute appendicitis

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A total of 155 consecutive patients with suspected acute appendicitis were studied to compare laparoscopic and conventional operations. Patients were not randomized: laparoscopy was performed when a suitably trained surgeon and laparoscopic instruments were available. Laparoscopic appendicectomy was attempted in 51 patients and was successful in 46 (90 per cent); all conversions to open operation were because of marked inflammatory adhesions around the appendix. There were no intraoperative complications. Reintroduction of normal diet and discharge from hospital occurred earlier after laparoscopic than open surgery ($P < 0\cdot05$)*. The requirement for analgesia after successful laparoscopic surgery was less than that after conventional appendicectomy, but the difference was not significant. The incidence of wound infection was reduced after the laparoscopic procedure* ($P = 0\cdot06$)*. It is concluded that laparoscopic appendicectomy is practical and may have advantages over conventional operation, although a randomized study is necessary.*

Laparoscopic appendicectomy was first described by Semm[1,2] in 1982, but until recently was popular in only a few centres[3,4]. However, the widespread introduction of laparoscopic surgery for gallstones has rekindled interest in the procedure. The major advantages of laparoscopic cholecystectomy are fewer complications and earlier recovery[5–8], although these are so dramatic that it has become difficult to perform comparative trials[9]. Hence the question arises whether the same benefits are available from laparoscopic appendicectomy.

The present study describes a series of appendicectomy operations performed during the 6-month period after the introduction of laparoscopic appendicectomy at this hospital. The aim was to assess the practicality of laparoscopic appendicectomy and to compare the results with those of the conventional operation.

Patients and methods

All patients were studied who underwent urgent operation for suspected acute appendicitis under the care of three adult general surgical firms during a 6-month period. Data were collected prospectively on the laparoscopic procedures and retrospectively for conventional open surgery. There were no specified criteria for selecting patients for laparoscopic appendicectomy. The type of operation was determined by the availability of laparoscopic facilities and surgical staff trained in laparoscopic procedures and the absence of the following contra-indications: pregnancy, extensive previous abdominal surgery, severe concomitant medical disease, and generalized peritonitis.

Premedication was prescribed at the discretion of the duty anaesthetist and was omitted in most cases. Prophylactic intravenous antibiotics were given in all cases: cefuroxime 1·5 g or 750 mg, ampicillin 500 mg and metronidazole 500 mg at induction of anaesthesia and three doses after operation. Operations were performed under general anaesthesia with the patient supine and without catheterization. Operating time was defined as that from induction of anaesthesia to adminstration of the reversing agent.

Operative technique

Laparoscopic appendicectomy was performed via three cannulas: a subumbilical one of 11 mm for the laparoscope, one of 11 mm in the left lower abdomen and one of 5 mm in the right lower abdomen, with occasional use of an additional cannula (5 mm) in the right mid-abdomen (*Figure 1*). If the appendix was too swollen to be extracted through an 11-mm cannula, this was replaced with one of 16 mm. The appendicular artery was controlled by diathermy or a metal clip (Ligaclip; Ethicon, Edinburgh, UK) and the appendix stump by a chromic catgut loop ligature (Ethibinder; Ethicon). The appendix stump was not buried, but saline lavage of the operative field and pelvis was performed at the end of the procedure. A single absorbable suture was placed in the rectus sheath at the umbilicus in most patients, and the skin wounds were closed with Steri-Strips (Ethicon).

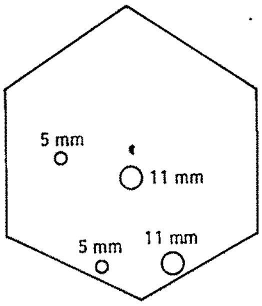

Figure 1 *Position of cannulas for laparoscopic appendicectomy. The 5-mm cannula in the right mid-abdomen is optional*

Open appendicectomy was performed through a transverse skin incision in the right iliac fossa and a muscle-splitting approach to the peritoneal cavity. The mesoappendix and appendix were ligated, and the appendix stump was buried in all cases. Lavage was not performed routinely, and the wound was closed in layers with interrupted nylon sutures to skin.

Postoperative management

The postoperative management, including the timing of reintroduction of diet and discharge from hospital, followed the normal practice of each operating surgeon. There were no predetermined differences between the two types of operation. All patients received intravenous fluids and intramuscular pethidine (approximately 1 mg/kg 3–4-hourly as required) for relief of pain. An outpatient follow-up appointment was arranged between 1 and 6 weeks after discharge from hospital, at which time data were collected on the incidence of wound infection.

Measurements of postoperative recovery were based on: quantity of intramuscular analgesia required, time to reintroduction of normal diet, and length of hospital stay. The requirement for analgesia after laparoscopic and conventional appendicectomy was compared using Student's *t* test, time to restart diet and time in hospital with the Breslow[10] test, and wound infection rates by Fisher's exact test.

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Results

Some 155 patients underwent surgery for suspected appendicitis during the 6-month study period. Six of these had generalized peritonitis and underwent laparotomy through a midline incision because of a wide differential diagnosis; these patients have been excluded from the results. Of the remainder, laparoscopic appendicectomy was performed in 51 patients by seven different surgeons (one consultant, four senior registrars, two registrars) and conventional appendicectomy in 98 patients by ten surgeons (two senior registrars, three registrars, five senior house officer grade). Patient details and main outcome are shown in *Tables 1* and *2* respectively.

Laparoscopic appendicectomy was successful in 46 patients (90 per cent) but failed in five. Indications for conversion to open operation (via a gridiron incision in all cases) were dense inflammatory adhesions around the appendix in four patients (all had had symptoms for >3 days) and inflammation involving the caecum in one. There were no conversions for haemorrhage or visceral injury, and no patient required a midline laparotomy incision. Three cannulas were used in 37 cases (73 per cent), while an additional port was required in the remainder. A 16-mm cannula was required to remove the appendix in 16 patients (31 per cent). At conventional appendicectomy the muscle-splitting incision proved inadequate in two patients (2 per cent) and required conversion to a muscle-cutting transverse incision.

The proportion of patients confirmed as having acute appendicitis was similar for both groups (*Table 1*). A normal appendix was left in two patients in whom laparoscopy showed pelvic disease; the appendix was removed in all patients who had open operations. There were more cases of perforated appendicitis among those having conventional operation (19 of 85 patients; 22 per cent) than among those having laparoscopy (four of 45; 9 per cent) ($P = 0{\cdot}04$, Fisher's exact test).

Patients with perforated appendicitis were treated routinely with a 5-day course of intravenous antibiotics. It is probable that their postoperative progress would have been affected by the more severe pathology and altered management. Thus, two sets of results are presented: those for all patients and those excluding patients with a perforated appendix (*Table 2*).

Postoperative course

One patient from each group was transferred to another hospital on the first day after operation to facilitate new admissions to the ward; these patients were excluded from the data on postoperative course. Four patients who had conventional appendicectomy failed to attend outpatient follow-up and are excluded from the data on wound infection.

Table 1 *Results of laparoscopic and conventional appendicectomy*

	Laparoscopic ($n = 51$)	Conventional ($n = 98$)
Age (years)*	32 (12–77)	26 (12–79)
Sex ratio (M:F)	2·4:1	2·0:1
Inflamed appendix†	45 (88)	85 (87)
Operating time (min)*	75 (35–185)	45 (17–110)
Total complication rate (%)	16	21

*Values are median (range); †values in parentheses are percentages

Of the laparoscopically treated patients, 31 per cent required no postoperative analgesia, compared with 17 per cent of the conventional group, but this difference was not statistically significant. Otherwise, there was little difference in the mean number of doses of postoperative analgesia between the two groups, even after exclusion of patients with perforated appendicitis (*Table 2*).

Diet was started earlier after laparoscopic surgery ($P = 0{\cdot}04$), a difference that remained significant when patients with a perforated appendix were excluded. Hospital stay was shorter after laparoscopic surgery ($P = 0{\cdot}03$). This trend was present after exclusion of cases of perforated appendicitis but was no longer significant (*Table 2*).

Postoperative complications

Wound infection was present in 12 (13 per cent) of 94 patients who attended follow-up after conventional operation; five had erythema only and seven a purulent discharge. Nine wound infections occurred in patients without perforation of the appendix. There was one possible wound infection in the laparoscopic group: the patient complained to her general practitioner of wound pain on day 8 but had neither redness nor discharge. She was treated with antibiotics. This difference is not significant ($P = 0{\cdot}06$), although the relative risk at 0·17 is far from the nominal value of 1 had the two treatments been equal.

There were three cases (6 per cent) of an intra-abdominal collection after laparoscopic appendicectomy and none after open operation. Two patients had persistent fever after operation and a third, discharged on day 2, presented on the eighth day with local signs. None of the patients had a mass, but ultrasonography showed a pericaecal fluid collection in each case; the largest collection measured 2 × 4 cm. Two patients were treated by needle aspiration and one managed conservatively. Resolution was confirmed by follow-up ultrasonography in all cases.

There were minor complications in a further four patients

Table 3 *Complications after appendicectomy*

	Laparoscopic ($n = 51$)	Conventional ($n = 98$)
Wound infection	1	12
Abdominal abscess	3	0
Prolonged pyrexia (>72 h) of unknown cause	1*	2
Chest infection	1†	1
Urinary retention	0	4
Intestinal ileus	1	2
Chest pain	1	0
Surgical emphysema	1*	0

*One patient had both symptoms; †patient with carcinoma of the bronchus

Table 2 *Postoperative course*

	All cases		Non-perforated appendicitis	
	Laparoscopic ($n = 51$)	Conventional ($n = 98$)	Laparoscopic ($n = 41$)	Conventional ($n = 66$)
Doses of intramuscular analgesia*	2·22(0·32)	2·48(0·21)	1·93(0·34)	2·44(0·22)
Time to restart diet (days)*	2·02(0·11)	2·36(0·11)†	1·89(0·10)	2·22(0·10)†
Time in hospital (days)*	3·76(0·25)	4·22(0·17)†	3·70(0·28)	3·85(0·16)
Wound infection rate (%)	2	13	2	14

*Values are Kaplan–Meier estimate of mean(s.e.m.). †$P < 0{\cdot}05$ (Breslow test) undergoing laparoscopic appendicectomy and nine having the conventional procedure (including four who developed acute retention of urine). The overall complication rate for the laparoscopic operation was 16 per cent and for the conventional operation 21 per cent (*Tables 1* and *3*); the difference is not significant.

Discussion

This study reports initial experience with laparoscopic appendicectomy performed by seven different surgeons, and shows the technique to be a viable alternative to conventional open surgery, with a success rate of 90 per cent. The advantages to patients treated laparoscopically were earlier reintroduction of diet and reduced hospital stay; the requirement for analgesia and wound infection rate were also both reduced, albeit not significantly so. There is likely to be some case selection in this series, as suggested by the smaller proportion of patients with a perforated appendix receiving the laparoscopic operation. However, the results remain encouraging when cases of perforation are excluded from the analysis.

The present results confirm those of a smaller study from Ireland conducted by a single surgeon[11], but which demonstrated a more dramatic difference between laparoscopic and open appendicectomy in terms of postoperative analgesia requirement and hospital stay. In the study of McAnena *et al.*, patients treated laparoscopically showed similar analgesia requirements to those in the present study but required a shorter median hospital stay of 2·2 days. In contrast, Irish patients treated by open operation required a median of 5 doses of analgesia and stayed in hospital for 4·8 days. Both values are greater than observed in the present study; the lack of significant differences may reflect unexpectedly good results in the present patients undergoing conventional surgery.

The present report recorded fewer complications in the laparoscopic group, notably the virtual elimination of wound infection which is the most frequent complication of appendicectomy and typically affects 17 per cent of patients[12]. Removal of the appendix through a cannula without it touching the wound edges is the likely explanation for this reduction. Although the greater incidence of perforated appendicitis among conventionally treated patients could have biased the results, the wound infection rate did not alter after exclusion of such cases. Low infection rates (4 per cent) were noted by McAnena *et al.*[11] while total absence was reported in a series of 388 laparoscopic appendicectomies from Germany[3]. An abscess complicated three of the present laparoscopic procedures; all were small and only one symptomatic. None of the surgeons performing laparoscopy in the present study buried the appendix stump, although Semm[13] has previously described the technique. Many surgeons leave the stump at open operation, and this does not affect outcome[14].

A likely argument against laparoscopic appendicectomy is that it takes too long, although operating time should fall as experience of the procedure is gained, as has been the trend with laparoscopic cholecystectomy[15]. Although the operation may take slightly longer, this is not a reason for avoiding laparoscopic appendicectomy, though it is essential to have the support of nursing staff and anaesthetists during the learning period.

Most of the present laparoscopic procedures were performed by surgeons of senior registrar grade, whereas conventional operations were most frequently undertaken by juniors of senior house officer grade. This discrepancy should not have been a source of bias as all surgeons were on a similar 'learning curve'. Experience in laparoscopic surgery had been gained from other laparoscopic procedures (including cholecystectomy) and porcine laparoscopic surgery including simulated appendicectomy (porcine salpingectomy). Two laparoscopic surgeons were present, one to assist the other, during initial operations. However, the need for a relatively senior surgeon to perform such a common procedure does have practical consequences. During the day, a junior surgeon may be available while more senior staff are committed to other duties. At night, a suitably experienced surgeon was not always available on call. If all appendicectomies are performed by senior staff, a valuable opportunity is denied to new trainees.

Although several authors have promoted the use of diagnostic laparoscopy for abdominal pain and suspected appendicitis[16–18], the extra time required and the lack of experience with laparoscopy have prevented many surgeons from adopting this technique despite a false-positive clinical diagnosis rate of 15–30 per cent[19]. With the ability to remove a diseased appendix laparoscopically, the diagnostic aspect becomes a more attractive proposition, although the present study does not provide data to evaluate this benefit of the approach. However, caution is required because the risk of false-negative diagnosis by the surgeon at operation does exist[16,20]; it is preferable to remove an apparently normal appendix unless another definite cause of the abdominal pain has been found.

Cosmetic results were not formally assessed. Although many surgeons claim that appendicectomy can be performed through a very small incision, this will not be so in every patient. In the ideal case for laparoscopic surgery, the instrument cannulas can both be placed in skin normally covered by pubic hair and the laparoscope port within the umbilicus. Such scars are invisible to all but close inspection. However, the right lower abdominal cannula, in particular, should be positioned to allow adequate retraction of the appendix and may have to be placed in a more visible site. The aim of operation is safe removal of the appendix, but this is likely to be achieved with better cosmetic results after laparoscopic than open operation.

In conclusion, laparoscopic appendicectomy is a practical alternative to the conventional operation and may offer a modest improvement in postoperative recovery. The benefits appear less marked than for laparoscopic cholecystectomy and a randomized trial is required to assess this procedure fully. The operation can be difficult in patients who present late. However, it is suggested that, whenever possible, if a surgeon experienced in laparoscopic surgery is available, there is little to be lost and a likely benefit to be gained by performing laparoscopy to confirm the diagnosis before proceeding to laparoscopic appendicectomy.

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Laparoscopic appendicectomy: a two-handed technique

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Most experience of laparoscopic appendicectomy has been gained using a modification of Semm's technique[1–3]; the appendix is drawn into a cannula at the right iliac fossa by the assistant while the surgeon dissects with the left hand and holds the camera in the right. This method feels unfamiliar to many laparoscopic surgeons. This paper describes a two-handed technique which mimics that of laparoscopic cholecystectomy; the procedure feels familiar to surgeons with experience in cholecystectomy and affords good training for those without.

Surgical technique

Figure 1 shows the positions of personnel and abdominal cannulas; the patient is positioned head-down with left lateral tilt. Pneumoperitoneum is created and the laparoscope inserted via an incision at the inferior umbilical margin. A 5-mm cannula (A) is inserted 1–2 cm above the right pubic tubercle and an 11-mm cannula (B) above the left. With the left hand, the surgeon uses a blunt-ended forceps in cannula A to manipulate the appendix and apply countertraction. Instruments held in the surgeon's right hand and inserted through cannula B are used for dissection. Using a pointed forceps or diathermy hook, the peritoneum over the mesoappendix is stripped away. The vascular pedicle is revealed as a bulge in the mesentery or at its free edge and a window is carefully created behind it. The pedicle is clipped and divided using instruments passed through cannula B. In some cases dissection can be kept close to the wall of the appendix and the mesentery stripped away, coagulating rather than ligating small vascular branches. Three endoloop ligatures (Ethibinder; Ethicon, Somerville, New Jersey, USA) are passed consecutively over the appendix and secured at the base. A loop is introduced into the abdominal cavity through cannula B, the grasping forceps in cannula A passed through it and the loop partly withdrawn to ensure it does not slip off the instrument. The appendix is regrasped and held under tension by the assistant while the surgeon tightens the ligature. The appendix is divided, leaving two ligatures on the stump, and the mucosa is cauterized. The appendix is withdrawn through cannula B. If it is markedly oedematous, the laparoscope is moved to this position and the umbilical cannula replaced with one of 16 mm diameter. Finally, the operative field is irrigated.

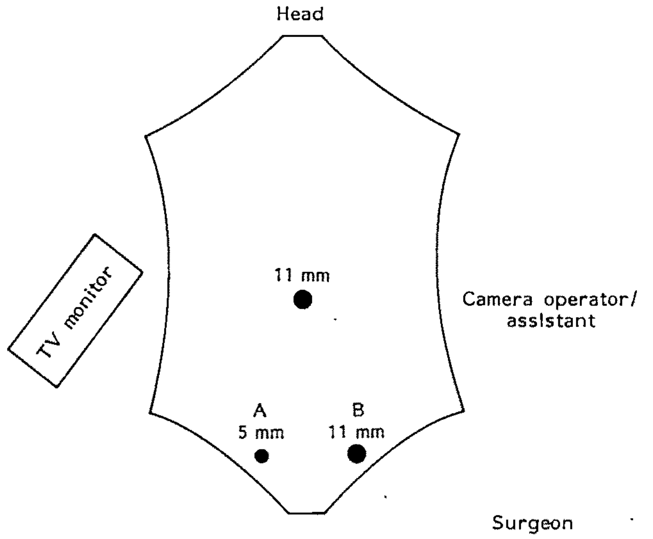

Figure 1 *Position of personnel and site of laparoscopic cannulas*

Discussion

Dissection of the appendix mesentery mimics that in Calot's triangle; the surgeon's left hand performs retraction while the right dissects. Placing the 11-mm cannula on the patient's left side, rather than directly over the appendix, allows the surgeon to use a variety of instruments with the right hand, including a clip-applying forceps; again, this is as for cholecystectomy. As both camera operator and surgeon stand on the same side, a familiar orientation is maintained and manoeuvres in which the video picture is a mirror image are avoided.

The low position of cannulas A and B affords an excellent cosmetic result. The bladder outline should be visualized before insertion; patients do not routinely undergo catheterization. In 100 operations no significant intraoperative complications have been encountered; conversion to open operation (9 per cent) has been for advanced pathology only.

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Function of ileal J pouch–anal anastomosis in patients with familial adenomatous polyposis

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Pouch function after proctocolectomy and ileal J pouch–anal anastomosis was assessed at 1 and 5 years in 41 patients with familial adenomatous polyposis. The mean(s.d.) stool frequency per 24 h decreased from 4·4(1·7) to 3·9(1·8) ($P < 0·05$)*, the mean(s.d.) nocturnal stool frequency fell from 0·6(1·0) to 0·3(0·6)* ($P < 0·05$)*, and the number of patients having nocturnal bowel movements decreased from 16 to seven* ($P < 0·05$). *At 5 years, only one patient still followed a strict diet* (versus *ten at 1 year,* $P < 0·05$) *and only two needed antidiarrhoeal medication* (versus *ten at 1 year,* $P < 0·05$). *There were no episodes of pouchitis or late reservoir-related complications. The function of ileal pouch–anal anastomosis improves over time in patients with familial adenomatous polyposis.*

In the treatment of patients with familial adenomatous polyposis (FAP), proctocolectomy and ileal pouch–anal anastomosis (IPAA) eliminates the risk of colorectal cancer because it removes at-risk mucosa[1,2].

Some advocate total colectomy and ileorectal anastomosis because the operation is easier to perform, avoids the need for a temporary stoma, has fewer postoperative complications and may have better functional results[3]. Lifelong surveillance of the rectal stump is required because of the risk of rectal cancer[4–7].

Protagonists of IPAA for patients with FAP claim that the postoperative complication rate is low, that pelvic sepsis and pouchitis are rare[8], that the risk of small bowel obstruction is similar to that following ileorectal anastomosis[9], that the need for a diverting loop ileostomy can sometimes be avoided[10] and that the early functional results are comparable to those obtained following ileorectal anastomosis[11].

Following IPAA for those with ulcerative colitis, pouch function improves in the first year after operation and remains stable thereafter[12]. No study has documented the long-term functional results of IPAA performed in patients with FAP.

The present study investigated the long-term clinical results in patients operated on for FAP in a single institution using the same operative technique. Changes over 5 years were studied.

Patients and methods

Patients

Patients undergoing ileal J pouch–anal anastomosis for FAP between September 1983 and July 1986 were studied. There were 49 patients but eight were excluded for the following reasons: emigration, two; IPAA performed after ileorectal anastomosis, two; unrelated death, one; death related to hepatic metastasis of a colonic cancer, one; IPAA performed for mid-rectal carcinoma, one; and pouch fistula requiring a long-term ileostomy prejudicing subsequent assessment, one.

Follow-up for 5 years was achieved in the remaining 41 patients.

Surgical technique

Colectomy, proximal proctectomy, excision of the distal rectal mucosa up to the dentate line, and construction of a stapled ileal J pouch with two limbs of 16–18 cm with a manual anastomosis to the dentate line was performed in all patients. A temporary diverting loop ileostomy was closed after 2 months.

Evaluation of pouch function

A data file was established for each patient to include: stool frequency, degree of continence, the need to wear a pad, the ability to release flatus safely, the ability to delay defaecation for > 15 min, perianal skin irritation, the need for a strict diet or antidiarrhoeal medication, and the occurrence of pouchitis.

Table 1 *Scoring system for the assessment and comparison of bowel function after ileal pouch–anal anastomosis*

	Score*		
Parameter	0	1	2
No. of stools per 24 h	$\leqslant 4$	5	$\geqslant 6$
No. of nocturnal bowel movements	0	1	$\geqslant 2$
Daytime incontinence	None	Minor	Gross
Night-time incontinence	None	Minor	Gross
Need to wear a pad	Never	$\leqslant 5$ days per month	$\geqslant 6$ days per month
Discrimination of flatus from stool	Perfect	Imperfect	Nil
Ability to delay defaecation > 15 min	Always	Usual	Rarely
Dietary restrictions	None	Minor	Extensive and permanent
Use of antidiarrhoeal medication	Never	$\leqslant 5$ days per month	$\geqslant 6$ days per month

*Overall function: $\leqslant 2$, good; 3–5, moderate; 6 or 7, tolerable; $\geqslant 8$, poor

Incontinence was described as none, minor (mucous staining of underwear with fewer than three episodes per week) or gross (three or more episodes per week or faecal staining).

These parameters were incorporated into a scoring system to facilitate comparison of pouch function (*Table 1*).

Pouchitis was defined as episodes of diarrhoea with or without blood loss accompanied by fever, malaise or other systemic symptoms that were present for $\geqslant 2$ days and responded promptly to oral antibiotics.

All patients were seen 3, 6 and 12 months after closure of the ileostomy and yearly thereafter until 5 years after operation. Those unable to attend were interviewed by telephone.

Statistical analysis

χ^2 and Student's t tests were used as appropriate. Comparisons of the distributions of ordinal variables were made with the rank sum test. $P < 0·05$ was considered significant.

Results

Forty-one patients (22 male, 19 female) were studied. The mean(s.d.) age at diagnosis of polyposis was 25(12) years and that at operation 28(9) years. Eight patients were > 40 years

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Table 2 *Stool frequency and faecal continence 1 and 5 years after ileal pouch–anal anastomosis in 41 patients with familial adenomatous polyposis*

	Length of follow-up	
	1 year	5 years
No. of stools per 24 h		
Mean(s.d.)	4·4(1·7)	3·9(1·8)*
Median	4	3*
No. of stools at night-time		
Mean(s.d.)	0·6(1·0)	0·3(0·6)*
Median	0	0
No. of patients with incontinence		
Daytime		
None	38	39
Minor	2	1
Gross	1	1
Night-time		
None	36	39
Minor	4	1
Gross	1	1

*$P < 0·05$ (Student's *t* test)

Table 3 *Long-term results following ileal pouch–anal anastomosis in 41 patients with familial adenomatous polyposis*

	Length of follow-up	
	1 year	5 years
Sexual dysfunction	0	0
Inability to delay defaecation >15 min	8	1
Need to wear a pad at night	2	1
Inability to discriminate flatus from stool	8	2*
Perianal skin irritation (>5 days per month)	8	3
Severe dietary restrictions	10	1*
Use of antidiarrhoeal medication	10	2*

*$P < 0·05$ (χ^2 test)

of age when surgery was performed. Fifteen patients were symptomatic (mean(s.d.) age at diagnosis 32(10) years) and 26 were asymptomatic call-up patients (mean(s.d.) age at diagnosis 18(5) years). No patient had continence, sexual or urinary problems before operation.

In six of the patients an abdominal desmoid tumour was present at operation (three patients) or was diagnosed later, after a mean delay of 23 months (three).

The mean(s.d.) follow-up was 67(9) (range 60–91) months.

The mean stool frequency per 24 h was 4·4 at 1 year and 3·9 at 5 years ($P < 0·05$). The mean night-time stool frequency was 0·6 at 1 year and 0·3 at 5 years ($P < 0·05$) (*Table 2*). The number of patients having nocturnal bowel movements decreased significantly (16 at 1 year *versus* seven at 5 years, $P < 0·05$). Daytime and night-time continence were similar at 1 and 5 years (*Table 2*).

Other functional parameters are detailed in *Table 3*. All patients could evacuate the ileal pouch spontaneously and none had sexual dysfunction or urinary problems. Pouchitis did not occur in any patient, although six experienced episodes of watery diarrhoea but without fever.

Figure 1 shows the results obtained at 1 and at 5 years using the scoring system to assess pouch function. The number of patients with a good result (score ≤2) increased from 22 to 34 ($P = 0·009$).

Age, sex and the presence of colorectal symptoms before operation did not influence stool frequency at 5 years. The mean(s.d.) stool frequency was higher in patients with than in those without an intra-abdominal desmoid tumour (5·5(2·7) *versus* 3·7(1·6) stools per 24 h).

Stool frequency at 5 years correlated with that at 1 year. Twenty-one patients had four or fewer bowel movements per 24 h at 1 year (mean(s.d.) 3·8(1·6)), and these had 3·4(1·5) bowel movements per 24 h at 5 years. Twenty patients with more than four bowel movements per 24 h at 1 year (mean(s.d.) 5·4(1·7)) had 5·1(1·8) bowel movements per 24 h at 5 years (group comparison at 5 years, $P = 0·003$).

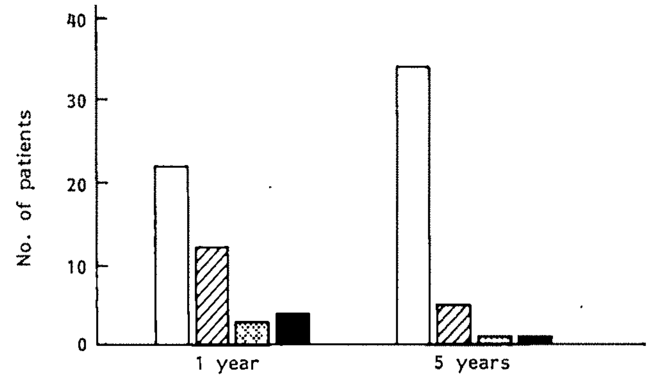

Figure 1 *Pouch function at 1 and 5 years after ileoanal anastomosis in 41 patients with familial adenomatous polyposis. Score* □, *good;* ■, *moderate;* ⊡, *tolerable;* ■, *poor. The scoring system is detailed in* Table 1

Discussion

Ileoanal anastomosis is now a widely accepted procedure for the treatment of FAP, particularly for the patient with a carpeted rectum or who is not available for follow-up[13]. The results of function following IPAA have been reported in numerous studies, but follow-up periods were short[14–16] and most patients were operated on for ulcerative colitis[14–18].

The present study shows that pouch function in FAP improved between the first and fifth years after operation.

Pouch function may improve with time because of selection bias[18]: pouches that fail usually do so within 2 years of creation, and this group of patients is often excluded from subsequent analysis. This is not the case in the present study because all patients were available for reassessment at 5 years.

Previous studies have shown that, as the reservoir becomes more capacious and compliant, and as coordination between the pouch and anal sphincter returns, clinical results improve[19,20]. This tendency for pouch capacity to increase with time[21] might explain the improvement noted in stool frequency.

Discrimination between flatus and stool was normal in 33 patients at 1 year and in 39 at 5 years. All these pouches were anastomosed to the dentate line after excision of the anal transition zone, supporting the contention that this area is not of major importance in the maintenance of good discrimination[22].

Incontinence is linked mostly to impaired internal sphincter function[23] and, as a consequence, is not susceptible to long-term improvement. Two factors that have been shown to influence overall pouch function adversely are postoperative sepsis and pouchitis[24]. These complications are unusual when IPAA is performed for FAP[8,25]. Pelvic sepsis and/or pouchitis was not seen in this series, and this was certainly of importance in the good pouch function observed.

There were no sexual problems reported following IPAA in the 22 men. In contrast to that in ulcerative colitis, rectal dissection in patients with FAP is easier because of the lack of perirectal inflammation, explaining the lower incidence of sexual problems associated with this indication[8].

Desmoid tumours are a manifestation of the disease that worsens the prognosis of patients with FAP. Ileoanal anastomosis does not seem to promote more abdominal desmoid tumours than ileorectal anastomosis. The 7 per cent rate reported in the present study following IPAA is similar to that of 9 per cent reported after ileorectal anastomosis[26], although abdominal desmoid tumours were detrimental to bowel function after IPAA in this study.

The present results at 5 years did not differ significantly from those reported following ileorectal anastomosis[11,27]. None of the patients in the present study had an endoscopic examination of the pouch at 5 years. Although adenomas can develop in pelvic pouches[27], to date no case of cancer in an ileoanal reservoir performed for FAP has been reported, in contrast to the established risk of cancer in the rectal stump following ileorectal anastomosis, which was found in one study[28] to be 5 per cent at 5 years.

In conclusion, pouch function in FAP improves with time and is comparable to that in other reports of bowel function following ileorectal anastomosis. The question of bowel function should not influence the choice between ileorectal anastomosis and IPAA in patients with FAP.

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Surgical workshop

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Use of cotton tapes in laparoscopic intestinal surgery

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Laparoscopic intestinal surgery has proven much more complex than that of the biliary tract. Operations on all parts of the colon and rectum have become feasible for certain benign conditions – limited Crohn's disease, endometriosis, rectal prolapse and the formation of ileostomy and colostomy – but safe manipulation is required for these freely mobile structures. It is necessary to grasp and move the intestine about the peritoneal cavity without causing trauma to it.

Currently available laparoscopic instruments such as graspers or Babcock-like devices risk injury to the bowel by exerting high pressure on a small surface area or through the leverage effect of these long instruments as they move the intestine about the abdominal cavity. Particularly when there are inflammatory changes in the bowel wall, direct instrumental manipulation may risk perforation and faecal contamination of the peritoneum.

This practical problem has been solved by laparoscopic placement of an encircling cotton umbilical tape, which allows effective atraumatic traction and reflection of the intestine.

Surgical technique

The mesentery adjacent to the intestinal wall is gently held with two endoscopic grasping instruments, using a third dissecting instrument equipped with cautery to electrocoagulate the peritoneum between the holding instruments. A mesenteric window is made at this point using the dissector, which is passed through the small window (*Figure 1*). A 6-mm wide cotton umbilical tape is introduced via a cannula into the abdominal cavity with one instrument, then grasped with the dissector and pulled through the mesentery. It encircles the bowel and is fixed using two Endoclips (US Surgical, Norwalk, Connecticut, USA), a Roeder loop tie or normal sutures. All traction and other movements can now be performed by grasping the tape instead of the intestine. Tapes may be placed rapidly approximately every 15 cm to allow mobilization of a section of large or small bowel.

The technique described is simple and allows easy retraction of the intestine without fear of injury. In addition, if the clip or tie is placed tightly against the bowel wall, the tape will become occlusive. The technique is particularly useful in mobilization of the right or left colon, and around the rectosigmoid for traction during laparoscopic rectal mobilization (*Figure 2*). Similar principles are being used to develop easy intracorporeal anastomotic techniques.

Acknowledgements

Figures 1 and *2* were drawn by Mr J. A. Pangrace.

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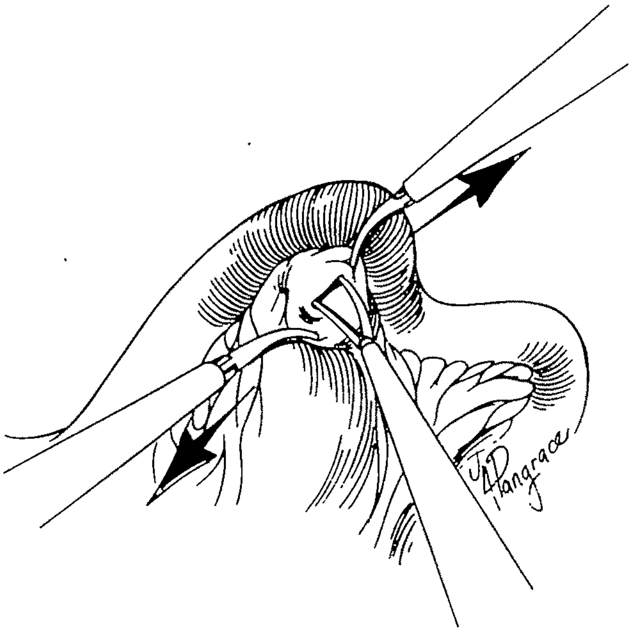

Figure 1 *A precise method of fashioning the mesenteric window is important. The mesenteric peritoneum immediately adjacent to the bowel wall is held taut in one direction while countertraction is provided by a second instrument (arrows)*

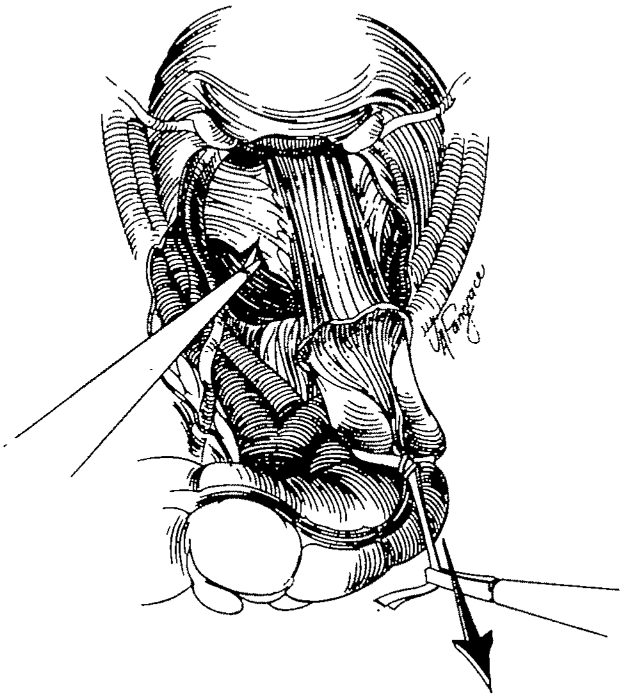

Figure 2 *A cotton tape encircling the rectosigmoid is clipped to itself then used for firm but safe rectal traction (arrow) during mobilization*

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Randomized trial of drainage of colorectal anastomosis

A prospective randomized trial was carried out to determine whether use of a high-pressure closed-suction intraperitoneal drain was associated with a reduction in morbidity rate after colorectal resection and to examine the influence of drainage on postoperative fluid collections. A consecutive series of 148 patients who underwent colonic or colorectal resection were randomized to receive no drain (n = *51*) *or a high-pressure closed-suction drain for either 3* (n = *47*) *or 7* (n = *47*) *days. Three patients were excluded. All patients underwent abdominal ultrasonography on days 3 and 7 and those undergoing left-sided colorectal resection* (n = *96*) *received a water-soluble contrast enema on day 7. The three groups of patients were similar in age, sex, diagnosis and the numbers of sutured and stapled anastomoses. The presence of a drain did not influence the postoperative morbidity or mortality rate. If the anastomosis leaked, neither faeces nor pus emerged from the drain. Ultrasonographic detection of a fluid collection was of no value: such collections bore no relationship to radiological or clinical leaks or the postoperative course. Routine use of a high-pressure suction drain after colorectal resection appears to be unnecessary.*

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Prophylactic drainage of the peritoneal cavity has remained controversial since it was first used by Sims in the late 1860s[1]. Advocates, such as Theodore Billroth[2], maintained that drains saved the lives of many patients who had undergone gastrointestinal surgery but others, such as Von Ott[3] and Delbert[4], argued that the procedure was useless and that drainage of the general abdominal cavity was impossible. For operations such as cholecystectomy, the consensus view appears to have moved away from routine drainage[5]. In contrast, and in spite of several theoretical arguments, most surgeons continue to advocate and employ routine prophylactic drainage after colorectal surgery[6].

The aims of this trial were to determine whether drainage after colorectal resection and primary anastomosis is associated with a decrease in the postoperative morbidity rate, and to establish whether an intraperitoneal drain is associated with an increased incidence of fluid collections.

Patients and methods

A consecutive series of 148 patients who underwent acute or elective resection of the colon or colorectum with primary anastomosis under the care of one consultant surgeon between January 1989 and April 1991 was entered into the study. One patient was excluded because the surgeon drained the splenic bed after splenectomy carried out in addition to colectomy, and two others were not randomized because of excessive faecal soiling.

Preoperative preparation of the bowel was identical in each patient and consisted of administration of two sachets of Picolax (sodium picosulphate; Nordic Pharmaceuticals, Feltham, UK), starting 24 h before operation. Each patient received prophylactic antibiotics with three doses of 1·2 g Augmentin Intravenous (co-amoxiclav; Beecham Research, Welwyn Garden City, UK) which began at the time of induction of anaesthesia and continued for 16 h. Patients who presented as emergencies underwent on-table colonic lavage and received Augmentin for 5 days after surgery. Operations were carried out by a consultant or registrar through a midline laparotomy unless a suitable pre-existing paramedian incision was present. Anastomoses were either sutured with a two-layer inverting technique using chromic catgut and linen or stapled with an EEA stapling instrument (Auto Suture, Ascot, UK). Forty-nine patients underwent right-sided colonic resection proximal to the splenic flexure and 96 left-sided colorectal resection distal to the splenic flexure. Thirty-one of the 145 patients (21·4 per cent) underwent non-elective surgery.

Randomization was carried out after completion of the anastomosis when the surgeon was about to begin closure of the abdomen. A proximal defunctioning stoma was not used. Each patient was allotted randomly into one of three groups; randomization involved opening of a sealed envelope drawn from a box of envelopes which had been filled on the basis of random numbers. Patients in the first group received no drain. Those in the second received a closed-suction high-pressure 0·25″ (6 mm) internal diameter Redivac drainage system (Biomed, Bridgend, South Glamorgan, UK), which was removed after 3 days. Patients in the third group received the same drainage system but this was removed on the seventh day. Drains were placed carefully such that the intraperitoneal end was close to the anastomosis but an attempt was made to interpose omentum between the drain and anastomosis where possible. The pelvic peritoneum was reapproximated where appropriate. All patients gave informed consent.

The volume and nature of any drainage fluid were recorded each day. Wounds were inspected daily by one of the authors. Abdominal ultrasonography was carried out in each patient on days 3 and 7 after operation. Scans were performed in real-time mode by radiographers unaware of the nature of the study. All patients in whom a left-sided anastomosis had been constructed (i.e. distal to the splenic flexure) were administered a water-soluble contrast enema (Gastrografin; Schering Health Care, Burgess Hill, UK) on the seventh day after operation to test the integrity of the anastomosis.

All patients were followed until at least 1 month after discharge from hospital and all complications recorded. A clinical leak was defined as discharge of faeces from the drain site or the presence of an abscess in close proximity to the anastomosis, or localized or generalized peritonitis with tenderness, fever and leucocytosis. A wound infection was defined by the discharge of pus. A chest infection was defined as the production of purulent sputum accompanied by appropriate clinical and radiographic changes.

Details of the patients in each of the three groups are given in *Table 1*.

Statistical analysis

All grouped data are expressed as median (interquartile range (i.q.r.)) and intergroup comparisons carried out using the Mann–Whitney *U* test or χ^2 test with Yates' correction[7]. Randomization was based on random number tables without stratification for age, sex, diagnosis or operation. It was estimated on the basis of audit of previous morbidity in the hospital that between 120 and 140 patients would be needed to give 90 per cent power to demonstrate an increase in morbidity of

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Table 1 *Details of patients*

	Drain		
	None ($n = 51$)	3 days ($n = 47$)	7 days ($n = 47$)
Sex ratio (M:F)	27:24	26:21	26:21
Median (range) age (years)	70 (56–77)	66 (55–74)	62 (58–72)
Anastomosis			
Sutured	39	38	28
Stapled	12	9	19
Ileocolic	16	15	14
Colocolic	21	20	16
High* anterior resection	5	4	9
Low* anterior resection	4	3	5
Ileorectal	4	3	2
Ileoanal	1	2	1
Surgeon			
Consultant	32	30	25
Registrar	19	17	22
Diagnosis			
Carcinoma			
Ascending colon	14	12	9
Transverse colon	3	2	2
Descending colon	9	7	4
Sigmoid colon	8	4	3
High rectal	5	3	7
Low rectal	4	3	6
Crohn's disease	2	6	10
Diverticular disease	2	4	3
Other	4	6	3
Operation			
Emergency	11	13	7
Elective	40	34	40

*Defined as anastomosis above or below the peritoneal reflection

10–20 per cent. The endpoint was anastomotic leakage and other morbidity and mortality. $P < 0{\cdot}05$ was considered significant.

Results

The patients in each group were similar except there were more with Crohn's disease allocated to receive drainage for 7 days and more with colonic cancer to receive no drain. The three groups were similar with regard to preoperative haemoglobin and albumin levels, white cell count, steroid use, Dukes' stage and need for perioperative blood transfusion.

There were ten deaths within 30 days of operation (6·9 per cent). Post-mortem examination showed the cause to be myocardial infarction in four patients, pulmonary embolus in two, septicaemia secondary to anastomotic dehiscence in three and massive gastrointestinal haemorrhage from gastric erosions in one. All the patients who died with anastomotic dehiscence and septicaemia had been allocated to receive a drain (one patient for 3 days, two for 7 days). The anastomosis was intact in the other seven patients who died after operation. Four of the ten deaths occurred in patients who had undergone non-elective surgery.

The incidence of complications, clinical or radiological anastomotic leak and mortality, and the length of hospital stay were not significantly different in the three groups (*Table 2*). A bad outcome, defined as death, anastomotic dehiscence or a major complication, was significantly more common in patients in whom a drain had been used for 7 days than in those who had not received drainage ($\chi^2 = 5{\cdot}55$, 1 d.f., $P < 0{\cdot}02$). However, the group receiving 7 days' drainage included a greater proportion of patients for whom the principal surgeon was the registrar than either of the other two groups (*Table 1*). This is important because it was found that the incidence of death and anastomotic dehiscence after operation by registrars was significantly higher than after operation by the consultant ($\chi^2 = 12{\cdot}55$, 1 d.f., $P < 0{\cdot}001$). There was no significant difference in complication rate between intraperitoneal and pelvic anastomosis.

Table 2 *Incidence of postoperative complications*

	Drain		
	None ($n = 51$)	3 days ($n = 47$)	7 days ($n = 47$)
Death	1 (2)	3 (6)	6 (13)
Clinical leak	3 (6)	3 (6)	5 (11)
Radiological leak	6 (12)	6 (13)	8 (17)
Wound infection	3 (6)	2 (4)	7 (15)
Chest infection	6 (12)	5 (11)	4 (9)
Length of hospital stay (days)			
Median	13	13	11
Interquartile range	10–14	10–15	10–13
95% confidence interval	11·6–14·7	12·0–17·2	10·2–17·0

Values in parentheses are percentages

Two patients developed a complication related to the drain: an infection occurred in one at the site of the drain stab wound and the drain could be removed from the abdomen of another only with great difficulty.

The total volume of drainage fluid was similar for patients receiving drainage for 3 and 7 days (median (i.q.r.) 370 (70–648) *versus* 333 (130–810) ml). The fluid was invariably serosanguinous.

Ultrasonography on day 3 demonstrated fluid collections in five of 51 patients without drainage compared with 11 of 94 with (P not significant). Similarly, repeat examination on day 7 demonstrated fluid collections in five of the 51 patients with no drain and ten of the 94 in whom a drain had been used (P not significant). The demonstration of a fluid collection on ultrasonography was not related to the presence of a clinical leak. A fluid collection was present on day 3 in one and on day 7 in three of 11 patients with a clinical leak. A collection was found on day 3 in 13 and on day 7 in 11 of 134 patients with no clinical leak. The median (i.q.r.) size of pelvic collection detected and measured by ultrasonography was 64 (24–64) cm^3 in patients with no drain compared with 48 (6–320) cm^3 in those with (P not significant).

Discussion

The main findings of this study are that the use of prophylactic drains after colorectal resection and primary anastomosis is not associated with a decrease in postoperative morbidity rate and if present, the drain failed to allow the egress of pus or faeces in the event of anastomotic dehiscence. Drains did not, therefore, confer any benefit to the patient. Serial ultrasonography detected fluid collections, but the presence of these did not necessarily indicate disruption of the anastomosis.

There have been few trials directed at identifying the value of drains after colorectal surgery[1–4,6,8,9]. Animal studies have shown that drains increase the rates of leakage, morbidity and mortality[9,10]. Ischaemia is a prime stimulus for adhesion formation, but without adhesions the anastomosis may leak. Physical separation of an ischaemic anastomosis from the omentum by a drain may be harmful[11]. The present trial confirms the results of previous studies. A prospective randomized trial[12] compared 49 patients with a corrugated Silastic (Dow Corning, Reading, UK) drain with 57 without a drain. Anastomotic leakage and wound infection rates, and outcome, were similar in the two groups. Another study of 60 patients with either a corrugated latex drain or no drain also failed to show a difference in the incidence of postoperative complications or anastomotic leakage[13].

The overall clinical leakage rate in the present study of 7·6 per cent was higher than rates reported by specialist colorectal centres but similar to those in comparable series[12,14]

The anastomotic technique used in each of the present patients was standardized but, as surgeons of different levels of experience from registrar to consultant were involved, the quality of the anastomosis will have varied.

The mortality rate in the present series at 6·9 per cent was higher than in other published prospective randomized trials of drainage. Those studies included only elective colorectal resection, whereas the present series included acute cases, mainly large bowel obstruction. This increased the eventual mortality rate in the present study, as four of the ten deaths were in patients who had undergone non-elective operations.

Gastrografin contrast studies were used in patients with left-sided anastomosis. Unlike others[12], the present authors have not experienced anastomotic breakdown as a result of the radiological technique, but care was taken to inform radiological colleagues of the level of the anastomosis when it was potentially close to the rectal tube. The higher rate of radiological leakage compared with the clinical rate has been noted before. Radiological leakage without clinical signs had no influence on the postoperative recovery.

It could be argued that the failure of drains to confer benefit resulted from failure to function. This seems unlikely, however, as the volume of drainage fluid was large and the drains were demonstrably patent at the time of removal. Drains did fail to function in the event of anastomotic dehiscence, in the sense that faeces and pus failed to escape down the drain but rather were retained within the abdominal cavity. However, in one patient, faeces did emerge through the main abdominal wound.

It has been suggested that drains may actually stimulate the formation of a collection[5] by encouraging a foreign-body reaction or inhibiting closure of the dead space. The presence of a fluid collection detected by ultrasonography was of no clinical relevance; such collections were presumably absorbed subsequently.

Drains may not only stimulate formation of serous fluid[15] but also increase postoperative pain. They may become infected and, rarely, lost into the abdomen or cause hernias[16,17]. Indeed, one patient in the present study with an infection at the site of the drain required 4 weeks of outpatient treatment before the infection resolved.

A high-pressure closed-suction Silastic drainage system was chosen for the following reasons. Although open corrugated systems are more likely to drain pus and faeces and may be safer, the patient is left with drainage fluid in contact with the skin and/or wet dressings. Nursing staff clearly favour the closed system. The suction drain was expected to be more effective in draining fluid than open corrugated drains, but the volumes recorded were no higher than those reported with the latter[16]. A potential disadvantage of Silastic in this context is that it stimulates formation of adhesions less than, for instance, latex. Increased adhesions may be of advantage near an anastomosis in the event of a leak but, conversely, they may occlude the drain and isolate it from the abdominal cavity.

Demonstrable benefit must be shown to justify the use of drains. It is unacceptable to insert a drain with its theoretical disadvantages to preserve the 'peace of mind' of the surgeon or as an excuse for lack of meticulous technique. These results suggest the abandonment of routine use of prophylactic drains after colorectal surgery.

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Gunshot wounds of the colon: role of retained bullets in sepsis

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The role in the development of local sepsis of retained bullets that hav passed through the colon was investigated. Of 84 patients with gunsho wounds of the colon, the bullet was retained in the body in 40 and ha left or was removed from the body in 44. The groups were similar wit regard to Revised Trauma Score, Injury Severity Score, Penetratin Abdominal Trauma Index and type of colonic trauma. The incidenc of major local complications was 5 per cent in patients with a retaine bullet and 7 per cent in those without. These results suggest that retaine bullets that have penetrated the colon do not contribute to local septi complications.

It has been suggested that bullets which have passed through the colon and remain lodged in the body are a focus of sepsis, and that they should therefore be removed. Poret *et al.*[1], in a retrospective study of 151 patients with gunshot wounds of the colon, found that the rate of sepsis in patients with retained bullets was 26 per cent compared with 16 per cent in those in whom the bullet had exited from the body. Although this difference was not significant, it was suggested that a retained bullet is a predisposing factor for infection. In the present prospective study the role of retained bullets in abdominal sepsis was investigated.

Patients and methods

A prospective study was performed at Baragwanath Hospital, Johannesburg, over a period of 15 months (in 1989–1990) on patients with gunshot wounds of the colon. The management policy for this type of colonic injury was debridement and primary repair, except in patients requiring colectomy for extensive colonic trauma or in those with massive faecal contamination. In these two situations, colostomy was performed. No effort was made to distinguish between low- and high-velocity injuries because this may be technically difficult or even impossible. Shock on admission, multiple colonic perforations, the anatomical site of the large bowel injury (right or left colon), delay >6 h, and high (>25) Injury Severity Score (ISS) or high (>15) Penetrating Abdominal Trauma Index (PATI) were not considered contraindications to primary repair[2]. At operation no attempt was made to locate and remove the bullet. However, if the missile was palpable, it was removed (these patients were included in the group with non-retained bullets). A closed drain was used, depending on the judgement of the operating surgeon. The abdominal wound was routinely closed primarily. Antibiotic prophylaxis with a third-generation cephalosporin was given for 48 h.

The following parameters were recorded: Revised Trauma Score (RTS), ISS, PATI, shock on admission (systolic blood pressure <90 mmHg), and the entrance and exit sites of the bullet. After operation patients were monitored for evidence of abdominal sepsis for a minimum of 10 days. Those who died within 48 h of operation were excluded from the study.

Results

Eighty-four patients fulfilled the inclusion criteria, comprising 81 male and three female patients of mean age 28·2 years. A further two died from associated major injuries within 48 h and were excluded.

In 40 patients (48 per cent) the bullet was retained in the body and in the remaining 44 (52 per cent) the bullet had left or was removed from the body. The two groups were similar with regard to RTS, ISS, PATI and shock on admission (*Table 1*).

The type of colonic injury and the management (primary repair or colostomy) were also similar in the two groups (*Table 1*). The majority of patients (77 per cent) had other associated intra-abdominal injuries, the most common bein to the small bowel (34 cases), the stomach (12), the liver (11 major vessels (six), duodenum (six), urinary system (six spleen (three) and biliary tract (two).

Table 1 *Trauma scores, site of injury and management of patients wit and without retained bullets*

	Bullet retained ($n = 40$)	Bullet not retained ($n = 44$)
Median (range) admission score		
Revised Trauma Score	7·8 (6·3–7·1)	7·8 (4·1–7·8
Injury Severity Score	26 (26–51)	26 (20–51)
Penetrating Abdominal Trauma Index	22 (8–57)	24 (12–43)
Site of injury		
Left colon	16	20
Right colon	8	14
Transverse colon	22	21
>2 colonic perforations	24	31
Surgical procedure*		
Primary repair	31 (78)	36 (82)
Colostomy†	9 (22)	8 (18)

*Values in parentheses are percentages. †Six patients in each grou had a colostomy because of resection; the remaining five had colostomy because of severe faecal contamination

All patients were followed for a minimum of 10 days afte operation; 65 per cent were followed for >10 days. Overal 12 patients (14 per cent) developed abdominal complication six (15 per cent) in the group with retained missiles and si (14 per cent) in the group without ($\chi^2 = 1·78$, 1 d.f $P = 0·55$). Missile track infection occurred in three case (4 per cent): one patient with a retained bullet and two withou Only five patients (6 per cent) developed severe complication two with retained bullets (5 per cent) and three witho (7 per cent) (*Table 2*). Only one patient developed an absces around a retained missile (2 per cent). This patient wa managed successfully with percutaneous aspiration. Th incidence of severe septic complications was 5 per cent i patients with isolated colonic trauma and 6 per cent in thos with other associated intra-abdominal organ injuries.

Discussion

Sepsis is the most common cause of postoperative morbidit and mortality following penetrating abdominal trauma. Goo surgical judgement and technique remain the most importa factors in the prevention of postoperative sepsis. Various ris factors have been incriminated in the development of abdomin

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Table 2 *Major local complications*

Patient no.	Injury	Type of colonic procedure	Bullet retained	ISS	PATI	Complications
1	Transverse colon, liver	Hartmann's operation	No	26	24	Faecal fistula*
2	Caecum, transverse colon	Primary repair	No	26	16	Faecal fistula*
3	Transverse colon, liver, haemothorax	Primary repair	No	35	16	Empyema of the chest
4	Sigmoid and transverse colon, stomach, spleen	Primary repair	Yes	26	35	Missile abscess
5	Transverse colon, diaphragm, haemothorax	Primary repair	Yes	26	15	Fistula*

ISS, Injury Severity Score; PATI, Penetrating Abdominal Trauma Index. *Closed with conservative management

sepsis: shock, high ISS, high PATI, gunshot wounds, colonic injuries and retained missiles[1,3–5]. Previous studies have shown that gunshot wounds, shock on admission, and high ISS or PATI are not significant risk factors for the development of abdominal sepsis[2,6]. Colonic trauma is the only significant factor; gunshot and knife wounds of the colon are associated with the same incidence of septic complications[6]. However, no distinction was made in these studies between retention or non-retention of bullets.

The role of retained missiles that have passed through the colon in the promotion of local sepsis is not clear. In a recent retrospective study of 151 patients, Poret *et al.*[1] found that those with retained bullets had a higher incidence of abdominal complications (26 per cent) than those with no retained missiles (16 per cent). Another interesting finding in that study was the high incidence of major septic complications (diffuse peritonitis, 21 per cent; intraperitoneal abscess, 24 per cent; extraperitoneal abdominal abscess, 56 per cent). These figures are probably the highest in the literature. The reported incidence of intra-abdominal abscess following colonic injury is between 2 and 12·7 per cent[2,7–9]. In the present study the incidence of abscess formation was 2 per cent in both groups. The minimum follow-up was only 10 days, although most patients were followed for longer. It is well known that sepsis may present later than 7–10 days after operation. None of the present patients returned with late sepsis; Baragwanath Hospital is the only tertiary care facility in the area.

In summary, the present study has shown that retained bullets that have penetrated the colon are not associated with a higher incidence of local septic complications than similar injuries where the missile has left the body or been removed. It is suggested that a retained bullet should be removed only if it can be located easily during operation.

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Effect of suture material on tumour cell adherence at sites of colonic injury

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In an experimental animal model, radiolabelled viable intraperitoneal adenocarcinoma cells adhered in similar numbers to normal rat colon and that injured by a 1-cm colotomy, with median cell counts of 7002 and 8602 respectively (P *not significant*)*. Repair of the colotomy with interrupted silk resulted in a significant increase in the median number of cells adhering to the injury site* (*21 888;* $P = 0.0001$ versus *normal colon*)*. Repair with Prolene had no effect on tumour cell adherence* (*a median of 7449 cells adhered;* P *not significant* versus *normal colon*)*. Tumour cell adherence at sites of colonic injury is dependent on the suture material used and not on the injury itself in this model. This may be important when choosing suture type for anastomosis in patients undergoing surgery for colorectal cancer.*

Experimental studies have demonstrated that tissue injury enhances tumour growth from locally implanted tumour cells or from cells reaching the site of injury via the circulation[1–4]. Tumour growth at sites of injury in colorectal cancer is observed at anastomoses, abdominal wounds, drain and colostomy sites, and on raw mucosal surfaces such as haemorrhoidectomy wounds[5–12].

The mechanism of enhanced tumour growth at sites of injury is poorly understood. The studies of Fisher *et al.*[2] suggested that such growth is related to the severity of the injury, which in turn appears to correlate with the number of circulating tumour cells that localize at the site of injury. It was found that fewer cells accumulated at clean surgical incisions, which were less likely to support tumour growth than sites of either mechanical (crush injury) or chemical trauma following intravenous or intra-arterial injection of viable tumour cells.

Certain suture materials are known to enhance anastomotic tumour growth in experimental animal models[13–16]. Differences in the ability of sutures to adhere to tumour cells have also been observed[17–19]. Adherence occurs maximally with braided materials such as silk and least with monofilament materials such as Prolene (Ethicon, Edinburgh, UK) or stainless steel (*Table 1*). The relative importance of suture material to tumour cell adherence in the presence of tissue injury, however, has not been investigated. The aim of the present study was to compare the adherence of viable intraperitoneal tumour cells to normal and injured colon and to injured colon repaired using different suture materials.

Materials and methods

Animals

Female Fischer F344 rats aged 12 weeks were used. All were housed under standard conditions and fed a pellet diet with water *ad libitum*.

Tumour cell line

$Mtln_3$ tumour cells, derived from a rat mammary adenocarcinoma, were donated by Drs Neri and Nicolson (M. D. Anderson Hospital, Houston, Texas, USA). Cells were cultured in 75-cm^2 or 160-cm^2 tissue culture flasks (Nunc, Kamstrup, Denmark) in medium consisting of equal parts Ham's F10 and Dulbecco's modified Eagle's medium (F10–MEM) with 10 per cent fetal calf serum (FCS). Cultures were maintained in 5 per cent carbon dioxide in humidified air at 37°C and moved a maximum of six times between thawing and experimental use to minimize phenotypic drift.

Preparation of radiolabelled tumour cells

Cells were cultured in 40 ml F10–MEM–FCS until 20–30 per cent confluent growth was obtained. The medium was then changed and 2 μCi $[^{125}I]$5-iodo-2′-deoxyuridine (IUDR; Amersham International, Chalfont, UK) added. Optimum radiolabelling of this cell line occurs using a concentration of 0·05–0·07 μCi IUDR per ml culture medium[20]. After 24 h cells were removed by first replacing the medium with 10 ml Hanks' balanced salt solution (Gibco, Paisley, UK) and then adding 5 ml 0·2 per cent trypsin and ethylenediamine tetra-acetic acid solution. When the cells had detached the trypsin was neutralized and cells washed twice with F10–MEM. Cell counts and viability were assessed using trypan blue exclusion and dilutions in F10–MEM adjusted to 1×10^6 cells in 0·2 ml medium. Radioactive counts were measured in 0·2 ml final dilution using a γ counter (Computamma; LKB–Pharmacia, Milton Keynes, UK).

Animal model

Under intraperitoneal anaesthesia with midazolam and fentanyl in water, 33 animals underwent laparotomy through a midline abdominal incision. A 1-cm colotomy was performed in the descending colon and repaired using four interrupted 5/0 silk sutures (Ethicon) (group 1S), four interrupted 5/0 Prolene sutures (group 1P) or four interrupted silk or Prolene sutures that were removed after 10 min when the anastomosis had sealed (group 1A). $[^{125}I]$IUDR-labelled $Mtln_3$ cells (10^6 in 0·2 ml medium) were then placed in the left paracolic gutter away from the anastomosis and left colon, and the laparotomy incision closed. After 1 h all animals were killed while still under anaesthesia, the anastomosis was excised, radioactivity measured and cell counts calculated. A 1-cm length of normal left colon was taken from all animals in group 1A to obtain control cell counts.

Controls for free $[^{125}I]$*5-iodo-2′-deoxyuridine*

Experiments were repeated using five animals in each group with free $[^{125}I]$IUDR in 0·2 ml cell-free F10–MEM. The concentration of label was calculated on the basis of radioactivity from previous washings of radiolabelled tumour cells. The purpose of this was to ensure that differences in radioactivity observed between groups represented differences in cell counts and not adherence of free $[^{125}I]$IUDR.

Table 1 *Adherence of W163 tumour cells to various suture materials*[17,18]

Material	No. of cells	*P**
Prolene	1 469(375)	—
Stainless steel	2 505(1440)	n.s.
Chromic catgut	3 110(1104)	<0.05
Nylon	4 939(1536)	<0.05
Silk	21 608(8135)	<0.0001
Vicryl	23 886(4584)	<0.0001

Values are mean(s.d.). Cell numbers adhering to 3-cm suture lengths were obtained using an *in vitro* assay with radiolabelled W163 adenocarcinoma cells[17]. * *Versus* Prolene; n.s., not significant

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Table 2 *Adherence of tumour cells to normal and injured colon*

Group	No. of rats	No. of cells*	P†
Normal colon	16	7002 (453–19263)	—
1A	16	8602 (115–28946)	—
1P	7	7449 (5028–17630)	n.s.
1S	10	21888 (11270–51187)	<0·005

*Values are median (range). †*Versus* normal colon and group 1A (Mann–Whitney *U* test with Bonferroni correction); n.s., not significant

Table 3 *Radioactive counts for normal colon and group 1S using free* [^{125}*I*]*5-iodo-2'-deoxyuridine*

Group	No. of rats	Counts*
Normal colon	5	7·5 (0–11)
1S	5	0 (0–5)

*Values are median (range). Counts for group 1S were not significantly different from those for normal colon (Mann–Whitney *U* test with Bonferroni correction)

Results

Effect of colonic injury

Tumour cell adherence at the site of injury in group 1A was not significantly different from that to normal or non-injured left colon taken from the same animals (*Table 2*). Adherence was similar whether silk or Prolene was used to appose the bowel wall in group 1A, with median cell counts of 8993 and 7685 respectively (*P* not significant) being observed.

Effect of suture material

Significantly increased tumour cell adherence occurred in group 1S compared with all other groups (Mann–Whitney *U* test with Bonferroni correction) (*Table 2*). In contrast, tumour cell adherence in group 1P was similar to that observed to normal colon (*Table 2*).

Effect of free [^{125}*I*]*5-iodo-2'-deoxyuridine*

Radioactive counts at the colotomy site sutured with silk were low and not significantly different from counts of normal colon (*Table 3*). Thus adhesion of free [^{125}I]IUDR could not account for the differences observed between group 1S and other groups.

Discussion

The present results demonstrate that colonic injury repaired with silk sutures results in the adhesion of significantly more intraperitoneal tumour cells than colonic injury alone or injury repaired with Prolene. Although it is difficult to extrapolate results from experimental models it is believed that this model resembles the clinical situation more closely than that used previously. There seems little doubt that viable exfoliated intraluminal and intraperitoneal cancer cells remain in significant numbers following potentially curative colorectal cancer surgery[21,22]. What is uncertain, however, is the role such cells play in the recurrence of colorectal cancer. This uncertainty is reflected in the diverse attitudes of surgeons to the prevention of tumour cell implantation during surgery for colorectal cancer[23].

Previous studies examining adhesion of tumour cells to various suture materials *in vitro* and *in vivo* have failed to take into account the effect of tissue injury on such localization[17–19]. Secretion of adhesive glycoproteins such as laminin and fibronectin by regenerating vascular endothelial cells and exposure of basement membrane collagen following surgical injury may provide an area that will attract and support the growth of increased numbers of tumour cells[17]. The study of Fisher *et al.*[2] indicated, however, that the degree of injury created may be important in this context and suggested that such factors play a significant role only when the wound is severe and caused by crushing or chemicals. Colonic injury created by sharp instruments and loosely applied sutures that were subsequently removed did not lead to the adhesion of any more tumour cells than to uninjured colon in the present study.

The period in which viable cancer cells were exposed to injured tissue was short in the present study. It is reasonable to assume that viable exfoliated cancer cells survive longer than 1 h in the bowel lumen or peritoneal cavity after surgery for colorectal cancer. Murphy *et al.*[3] demonstrated the presence of viable cancer cells by bioassay in many organs for up to 24 h after intra-arterial injection. Likewise, Fisher *et al.*[2] demonstrated significantly increased counts in areas of tissue injury 24 h after intravenous or intra-aortic injection of viable tumour cells. The increase, however, was only marginally greater than that obtained after 1 h in surgically traumatized animals, suggesting that, under these conditions at least, the majority of tumour cells become localized within the first hour of exposure.

Increased trapping of tumour cells is probably only one factor explaining enhanced tumour growth at sites of tissue injury. Increase in growth factor levels in response to healing of injured tissue may also be important in that viable cancer cells might achieve a proliferative advantage by being favourably positioned with respect to cells that are involved in the healing process and act as a paracrine source of growth factors[24]. Work by Loizidou and associates[25] supports this hypothesis; it was demonstrated that fibroblasts from regenerating liver promoted significantly more tumours from a colorectal cancer cell line inoculated subcutaneously in nude mice and tumours were tenfold larger than in controls. Similar results have also been demonstrated for breast cancer cell lines using breast and skin fibroblasts[26].

The present study demonstrates in an experimental model that the suture material used to repair an injury is more important than the injury itself in promoting adhesion of intraperitoneal tumour cells to a colonic anastomosis. Because colorectal cancer has a high incidence of local recurrence after resection, it is recommended that the anastomosis is created using a suture with a low potential for tumour cell adherence.

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Detection and enumeration of circulating tumour cells in colorectal cancer

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Immunocytochemistry was used in parallel with conventional cytology to detect circulating malignant epithelial cells in 42 patients undergoing resection for colorectal cancer. Preoperative peripheral and peroperative mesenteric venous blood samples were taken. Tumour cells were isolated on a density gradient and cytospins prepared. Slides were stained by conventional cytology (May–Grünwald–Giemsa) and by an indirect immunoperoxidase technique with the anticytokeratin antibody K_G 8.13. Using conventional cytology, definite morphological evidence of malignancy was observed in three patients and suspicious features in a further seven. Immunocytochemistry confirmed these findings in all three of the malignant but in only one of the suspicious cases. Counts of immunostained cytospins showed the concentration of tumour cells in blood samples from these four patients to be in the range 0–954 cells/ml. This study supports the use of immunological markers to detect and enumerate malignant cells. This method provides a powerful tool to investigate one aspect of the metastatic process.

The development of a metastasis is a stepwise process in which the intravasation and circulation of malignant cells precedes their entrapment, invasion and progressive growth in the host organ[1]. In colorectal cancer, invasion of venous radicles of the portal system is associated with the development of hepatic metastases[2]. Theoretically, therefore, the identification and enumeration of circulating malignant cells in the portal system may be used to predict patients at risk of developing hepatic secondaries.

Using conventional cytology, the incidence of circulating malignant cells in patients undergoing resection for colorectal cancer ranges from 25 to 67 per cent[3–6]. This wide variation in incidence may be the result of difficulty in distinguishing tumour cells from plasma cells and the 'atypical' mononuclear cells occasionally found in normal blood[6,7].

To overcome these diagnostic difficulties, Glaves *et al.*[8] introduced an immunological marker to identify circulating epithelial cells. In the presence of a tumour, such cells may be inferred to be malignant cells circulating as a result of venous invasion. The anticytokeratin monoclonal antibodies stain epithelial[9] but not endothelial cells or those of haemopoietic origin[10]. In addition, stromal cells are not stained as they are of mesenchymal origin and express vimentin as the major intermediate filament protein[10].

The present study compared conventional cytology with an immunological method to detect and enumerate circulating tumour cells in patients undergoing resection for colorectal cancer.

Patients and methods

Patients

Forty-two patients with colorectal cancer were studied: 23 men and 19 women with a mean age of 67 (range 34–87) years.

Blood samples

Two samples were removed: a preoperative sample taken from an antecubital fossa vein without a tourniquet, and a peroperative sample from the mesenteric vein draining the tumour, taken after tumour mobilization. A full blood count was performed to determine the concentration of mononuclear cells.

Preparation of cytospins

Blood was diluted with an equal volume of tissue culture medium, layered on to 5 ml density-gradient medium (Histopaque-1077; Sigma Chemicals, Poole, UK) and centrifuged at 400*g* using a cytospin (Mistral 1000; Mistral, Loughborough, UK) for 30 min. The interface layer was harvested, washed twice in E4 tissue culture medium (Department of Zoology, University College London) and spun at 400*g* for 10 min before the cell pellet was resuspended in 1 ml medium and diluted to obtain a suspension of approximately 1×10^6 cells/ml.

Staining

All reagents were obtained from Merck, Poole, UK unless otherwise stated. Six cytospin preparations from each blood sample were air-dried and stained using a May–Grünwald–Giemsa method. A further six preparations were stained by a standard indirect immunoperoxidase technique[11] using the anticytokeratin monoclonal antibody K_G8.13 (Sigma). This is a broadly reactive anticytokeratin antibody that recognizes most human keratins but does not cross-react with any other type of intermediate filament. It was selected from a panel of six antibodies in preliminary studies that included anticytokeratins NCL 5D3, RCK 102 and CAM 5.2, and epithelial cell membrane markers AUA1 and Ber-EP4.

Cells were fixed in acetone, endogenous peroxidase activity was blocked with 0·3 per cent hydrogen peroxide in methanol for 30 min, and anticytokeratin K_G8.13 primary antibody applied for 60 min to five slides. A secondary rabbit antimouse antibody conjugated to horseradish peroxidase (Dakopatts, Glostrup, Denmark) was applied for 45 min. A brown product was formed by the reaction of horseradish peroxidase in 3,3′-diaminobenzidine tetrahydrochloride. Nuclei were counterstained with haematoxylin.

The SW480 colorectal cancer cell line[12] was used as a positive control. A sixth slide was prepared from each sample with no primary antibody, to act as a negative control. In addition, antecubital and mesenteric vein blood samples were collected from seven patients undergoing colectomy for benign disease. An antecubital vein sample was also taken from 15 volunteers.

The May–Grünwald–Giemsa and immunoperoxidase cytospin preparations were examined by a consultant cytopathologist on separate occasions and without knowledge of the patients' identities or clinical details. With this 'blind' method of assessment, information from one preparation could not be used to reinforce or help with the interpretation of the other.

The criteria used to identify a tumour cell on conventional cytology were: (1) large hyperchromatic nucleus; (2) irregular chromatin pattern; (3) high nuclear:cytoplasmic ratio; (4) abnormal mitoses; and (5) prominent nucleolus. Tumour cells on antibody-stained slides were

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identified by their brown colour on staining with the immunoperoxidase technique. In addition to the cytological assessment, the concentration of tumour cells (when identified) was established according to the method described below.

Enumeration of tumour cells

The assumption was made that both tumour and mononuclear cells were deposited with equal efficiency in the interface layer following density-gradient centrifugation. The ratio of tumour cells to mononuclear cells (lymphocytes and monocytes) in the interface layer should thus not differ significantly from that in whole blood. This in turn would allow the concentration of tumour cells in whole blood to be determined from the ratio of tumour cells to mononuclear cells observed on prepared cytospins. The method used to calculate the number of tumour cells is set out in the equation:

$$[T] = \frac{[M] \times T_c}{M_c}$$

where $[T]$ is the tumour cell concentration, $[M]$ the monocyte concentration, T_c the tumour cell count on cytospin(s) and M_c the monocyte count on cytospin(s).

Validation. Six 5-ml aliquots of volunteer blood were used, one to determine the concentration of mononuclear cells (lymphocyte and monocyte counts). To four of the remaining five samples, SW480 tumour cells were added so that the concentration of tumour cells within each was respectively 10^1, 10^2, 10^3 and 10^4 per ml. No tumour cells were added to the fifth sample, which acted as a control. Each of the five density gradients was then centrifuged, the interface layer harvested and washed, and cytospins made and stained with the anticytokeratin antibody as described. The relative numbers of tumour and mononuclear cells on each of the six cytospins were determined and the combined values substituted in the equation to calculate the tumour cell concentration.

This experiment was repeated using five different samples of volunteer blood.

Results

Patients

The clinical and histopathological details of the ten patients with positive immunocytochemistry and/or atypical conventional cytology are shown in *Table 1*. The remaining 32 patients had negative results. These 32 comprised 19 men and 13 women of mean age 68 (range 34–87) years. Two tumours in this group were classified as Dukes' A, 17 as B, ten as C and one as 'D'; one was recurrent and one not resected. Seven tumours had extramural vascular invasion.

Detection of malignancy

Using the criteria described for conventional cytology and/or positive immunocytochemical staining, circulating tumour cells were found in six samples from four patients.

Comparison of conventional cytology and immunocytochemistry

Biopsies taken from frozen sections of the tumours and stained with K_G 8.13 were positive in all cases, confirming expression of the antigen by the tumour.

A total of 81 blood samples (42 antecubital, 39 mesenteric vein) were taken. The results are presented in *Table 1*, with a comparison of conventional cytology and immunocytochemistry shown in *Table 2*. Using conventional cytology, definite evidence of malignancy was seen in three samples and

Table 2 *Comparison of conventional cytology and immunocytochemistry of all blood samples*

	Conventional cytology			
Immunocytochemistry	Malignant	Atypical	Benign	Total
Positive	3	2	1	6
Negative	0	7	68	75
Total	3	9	69	81

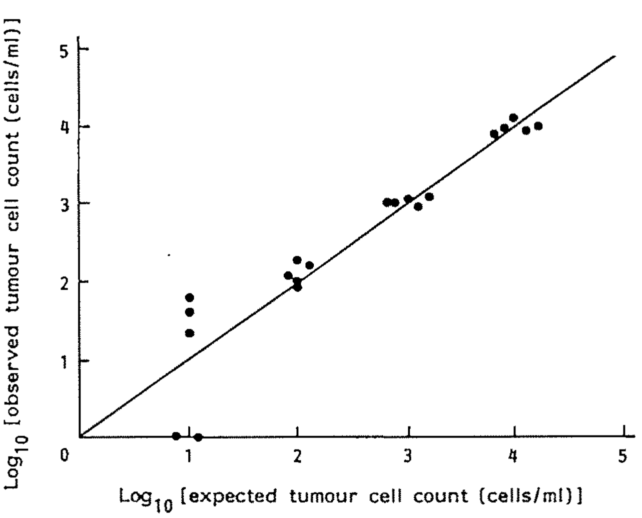

Figure 1 *Correlation between the observed and expected tumour cell concentrations (expressed logarithmically) of the* in vitro *seeding experiment*

Table 1 *Comparison of conventional cytology and immunocytochemistry of preoperative antecubital and peroperative mesenteric venous blood samples with respect to clinical and pathological variables*

								Venous sample			
								Antecubital		Mesenteric	
Patient no.	Age (years)	Sex	Operation	Tumour site	Dukes' stage	Differentiation	Vascular invasion	Cytology	Antibody	Cytology	Antibody
5	81	F	Anterior resection	Rectum	A	Moderate	–	±	–	–	–
8	72	F	Right hemicolectomy	Ascending colon	C	Moderate	+	±	–	±	–
9	56	F	Anterior resection	Rectum	C	Moderate	+	+	+	±	+
10	68	F	No resection	Rectum				+	+	n.t.	n.t.
11	73	F	Abdominoperineal resection	Rectum	B	Poor	–	±	+	–	+
12	60	M	Right hemicolectomy	Ascending colon	C	Poor	–	±	–	–	–
15	60	F	Anterior resection	Rectum	B	Moderate	+	–	–	+	+
22	62	M	Anterior resection	Rectum	A	Moderate	+	–	–	±	–
33	67	M	Left hemicolectomy	Sigmoid	C	Moderate	–	–	–	±	–
42	57	M	Sigmoid colectomy	Sigmoid	'D'	Moderate	–	–	–	±	–

n.t., Not tested; ±, atypical

Table 3 *Tumour cell concentrations*

Patient no.	Venous sample	White cell count (× 10^6/ml)	Mononuclear cell count (× 10^6/ml)	Tumour:mononuclear cell ratio	Tumour cell count (cells/ml)*
9	Antecubital	3·5	1·16	6:35179	197 (72–428)
	Mesenteric	3·8	1·91	26:52020	954 (622–1397)
10	Antecubital	4·5	1·98	2:97731	40 (5–146)
11	Antecubital	7·7	1·92	2:58690	65 (8–237)
	Mesenteric	8·4	1·40	2:30452	92 (11–332)
15	Antecubital	—	—	—	0
	Mesenteric	10·5	6·09	1:78746	77 (2–431)

*Values are mean (95 per cent confidence interval)

features suspicious of malignancy in a further nine. Immunocytochemistry confirmed the findings in all three of the morphologically malignant samples but in only two of the nine morphologically suspicious cases. In addition, one of 69 samples that showed no malignant cells using conventional cytology was positive for K_G 8.13 (mesenteric vein sample of patient 11). The antecubital vein sample from this patient had morphologically suspicious cells staining positively with immunocytochemistry. No positively stained cells were found in any of the non-malignant samples or in any of the negative controls.

In vitro *quantification*

No control sample stained positively with the K_G 8.13 antibody, confirming that it did not bind to cells of haemopoietic origin. The results for all five experiments are shown in *Figure 1*. Apart from two cases in which 10^4 tumour cells were seeded, there was no significant difference between observed and expected ratios of tumour cells to mononuclear cells. These two values lie very close to the regression line (*Figure 1*). This technique was therefore considered a reasonable method by which the numbers of circulating cells in patients could be estimated.

In vivo *quantification*

The results are shown in *Table 3*. The concentration of tumour cells in samples from the four patients ranged from 0 to 954 cells per ml blood. In two patients (nos 9 and 11), tumour cells were found in both peripheral and mesenteric vein blood samples (antecubital vein: 197 and 65 cells/ml; mesenteric vein: 954 and 92 cells/ml respectively). In another patient (no. 10), tumour cells were found in the peripheral sample (40 cells/ml) and no mesenteric vein sample was obtained. In another patient (no. 15), tumour cells were detected only in the mesenteric vein sample (77 cells/ml).

Discussion

Historically, conventional cytology has been the only method for the detection of circulating tumour cells. There has to date been no report of the use of immunological markers alongside conventional cytology to detect circulating cells from a solid tumour. In a recent study, however, blood samples from eight of ten patients undergoing nephrectomy for renal adenocarcinoma contained cells staining positively with the monoclonal anticytokeratin antibody[8] AE3. Although these cells were considered malignant, their morphology was not assessed by conventional cytology.

Using conventional cytology, features of malignancy were found in six of the present antecubital samples and in six of those from the mesenteric vein. When strict morphological criteria were applied, only two of the peripheral vein samples and one of those from the mesenteric vein were considered to contain definitely malignant cells. These numbers are considerably lower than those obtained using conventional cytology reported in previous studies of patients undergoing resection for colorectal cancer[3–6]. This discrepancy may be related to variation in the interpretation of morphological features when using conventional cytology[13].

Seven samples were considered to be atypical using conventional cytology but immunocytochemistry showed only haemopoietic cells; this may explain the high rate of apparently malignant cells reported in previous studies. Melanoma cells have recently been detected in peripheral blood by reverse transcription and the polymerase chain reaction[14]. This technique may prove useful in colorectal cancer.

Are circulating malignant cells diagnostic of metastasis? In animal systems, and probably also in humans[8,15], the implantation of cancer cells from peripheral blood is inefficient[16], with fewer than 0·1 per cent of circulating tumour cells surviving to form secondary growths in a murine model[17], probably because circulating tumour cells are susceptible to various host defences[18]. In addition, only part of a heterogeneous population of tumour cells is capable of implantation[19]. The prognostic significance of circulating tumour cells in colorectal cancer is unclear, with reports of a better prognosis[20], a worse prognosis[21] or no significant difference in survival[22]. These discrepancies may be the result of using cytology alone; the combined approach described in the present study should resolve such difficulties.

Is the yield of circulating malignant cells related to the effort spent in their detection? Multiple lymph node sectioning and monoclonal antibody staining detect occult metastatic disease after resection for colorectal cancer[23]. Whether cells traversing the sinusoids of a lymph node would lead to downstaging of a case or whether these cells are irrelevant in prognostic terms has yet to be determined; analogous reasoning can be applied to such cells circulating in the bloodstream. Cancer cell release is an intermittent process[8,24,25], which makes it inevitable that sampling errors will occur when only single-point blood samples are taken[8]. It is likely that multiple-point or larger volume sampling would increase the yield of malignant cells. This is reflected in a recent study that found cytokeratin-positive cells in single bone marrow aspirates of 42 (28 per cent) of 150 patients undergoing resection for colorectal cancer[26].

It was surprising that no malignant cells were detected in the blood of two patients with liver metastases. This is probably related to single-point sampling. Malignant cells were found in two of 11 patients with and in one of 29 without vascular invasion. (No information on such invasion was obtained for patient 10 – one of the four malignant cases – as the tumour was not resected.) These findings support recent studies in which extramural venous invasion lost prognostic value in a multivariate analysis model[27–30].

Detection of circulating malignant cells might also reveal residual or recurrent disease after curative resection and might be tested against carcinoembryonic antigen monitoring. Further work will be required to determine optimum sample numbers and intervals before such comparison will be possible.

It is concluded that the application of strict morphological criteria for malignancy in combination with an immunocytochemical method helps to identify circulating malignant cells in patients with colorectal cancer. This parallel approach advances previous studies in two ways. First, the morphological parameters distinguish cells exhibiting definite from suspicious features of malignancy, and the immunological probe establishes the origin of these cells. Second, immunocytochemistry facilitates the quantification of tumour cells.

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Colonoscopic follow-up after resection for colorectal cancer: a selective policy

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A policy of selective colonoscopy after resection for colorectal cancer was evaluated to assess the benefit of detecting missed synchronous and metachronous tumours in patients under 70 years of age with a good prognosis, and the possible risk of missing such lesions in those not screened. With preoperative barium enema and palpation at laparotomy, synchronous cancers and adenomas were found in 2 and 28 per cent, respectively, of 275 consecutive patients undergoing resection. Eighty-five patients were selected for postoperative colonoscopy, which was repeated at least once in 32, there being a total of 60 repeat examinations. Adenomas, but no cancers, were found in 19 patients (22 per cent) on first screening, but on repeat colonoscopy early metachronous cancers were detected in three patients (9 per cent) and adenomas on 21 examinations (35 per cent). Only one of the patients followed by clinical examination developed a symptomatic tumour. This suggests that postoperative colonoscopy is unlikely to benefit the majority but may be extremely important for young fit patients with continuing polyp formation who are at high risk of developing metachronous cancer.

The role of colonoscopy in the management of colorectal cancer remains controversial. Although many surgeons consider colonoscopy mandatory for all patients before resection for colorectal cancer and advise frequent endoscopic surveillance after surgery, others are reluctant to adopt such a policy. The arguments for colonoscopy are persuasive since it is clearly established that a significant minority of patients will have synchronous neoplasms while others will develop metachronous tumours[1,2]. Preoperative colonoscopy may influence the planned resection in 9–16 per cent of cases[3–5] and prevent synchronous tumours being missed, while postoperative colonoscopy may detect early recurrences that are amenable to resection and permit removal of metachronous adenomas before the development of invasive carcinoma. The expectation of these endeavours is that survival following resection for colorectal cancer will be improved.

However, the implementation of a policy of colonoscopy before and after resection would subject patients to multiple invasive investigations with an associated morbidity without proven benefit and would impose considerable stress and cost on existing endoscopy services. Consequently, the authors perform colonoscopy only after surgery and only in selected patients. To assess the value of this policy, and to ensure that selection has not adversely affected the care of those not screened, the outcome for all patients undergoing resection for colorectal cancer has been analysed.

Patients and methods

Initial treatment

Between 1981 and 1989, 275 patients underwent resection for colorectal cancer under the care of one surgeon. There were 154 men and 121 women with a median age of 71 years. One patient had chronic ulcerative colitis but none had familial adenomatous polyposis. Four patients had already undergone resection for colorectal cancer without prolonged follow-up 14, 19, 20 and 23 years previously when aged 66, 63, 49 and 51 years respectively.

For 41 patients, in whom resection was performed within 48 h of admission to hospital, complete preoperative assessment of the colon was not possible. For the remainder, in whom elective surgery was performed, double-contrast barium enema was used almost exclusively to investigate the large bowel. Colonoscopy was employed in only five patients and fibreoptic sigmoidoscopy with or without barium enema in 19. Forty-six patients with carcinoma of the rectum underwent surgery without either barium enema or colonoscopy. Manual examination of the bowel was performed at laparotomy in all patients.

Twenty-two procedures were palliative either because of irresectable hepatic metastases (17 patients) or macroscopic residual tumour (five), and 11 patients (4 per cent) died in hospital. Consequently, 242 patients with residual colon or rectum who had received potentially curative surgery, including one who underwent hepatic resection, were available for follow-up.

Clinical follow-up

All patients were examined clinically at 6-monthly intervals for 2 years, then annually thereafter where practical. The examination included rigid sigmoidoscopy but no other routine diagnostic tests. Additional follow-up information was obtained from general practitioner records.

Endoscopic follow-up

The surveillance protocol evolved during the study period. Surveillance was targeted at those aged <70 years although exceptions were made. Patients $\geqslant 70$ years of age were included when they were considered exceptionally fit, while some younger patients refused colonoscopy and were followed clinically. At the beginning of the study, a few patients later considered eligible were not offered surveillance. To date, 80 patients (13 $\geqslant 70$ years of age) have had complete colonoscopic examination on at least one occasion during postoperative follow-up, with a further five having undergone only partial examination because of difficulty negotiating the entire residual colon.

As the risk of recurrent disease is greatest[6] in the first 2 years, patients with Dukes' C tumours were usually offered screening only if there was no evidence of recurrence after approximately 2 years. Consequently, 57 patients underwent initial colonoscopy within 2 years of resection and 28 after 2 years. Patients were offered subsequent colonoscopy every 2 years after the initial screening. To date, 32 patients have had two colonoscopies; 14 of those have had three or more as part of the routine surveillance protocol or because successive examinations revealed new polyps. The overall success rate for visualizing the entire residual colon was 92 per cent.

Statistical analysis

The Mann–Whitney *U* test, Fisher's exact test and χ^2 analysis were used for statistical comparisons. $P < 0{\cdot}05$ was considered significant.

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Results

Synchronous lesions

In addition to the symptomatic cancer preoperative double-contrast barium enema demonstrated a synchronous carcinoma in one patient and synchronous adenomas in nine. The synchronous carcinoma modified the planned resection. The adenomas were removed endoscopically in six patients and in the resection specimen in three. No further tumours were found at laparotomy.

Resection specimens were submitted to histological examination and the cancers staged using Dukes' classification. The distribution of primary tumours is shown in *Figure 1*. Five specimens contained unsuspected synchronous cancers and 67 synchronous adenomas, giving overall rates of detected synchronous cancer and adenoma of 2 and 28 per cent respectively. *Table 1* shows the number of each type of resection performed and the prevalence of synchronous adenoma and cancer within the resection specimens.

Metachronous lesions

Fifty-seven asymptomatic patients underwent surveillance colonoscopy within 2 years of surgery to detect missed synchronous or early metachronous lesions. Although these patients were younger than those followed clinically, the Dukes' class distribution and prevalence of synchronous adenomatous polyps were not significantly different (*Table 2*).

No cancers were detected at this initial screening but adenomatous polyps were found in 14 patients (25 per cent) and metaplastic polyps only in a further three. Two of the 17 patients had not undergone preoperative barium enema. Fifteen patients underwent successful endoscopic polypectomy and two required reoperation. A 70-year-old man underwent right hemicolectomy to remove a large villous adenoma in the caecum that was discovered by colonoscopy 15 months after left hemicolectomy for a Dukes' C carcinoma of the splenic flexure. The initial resection specimen had also contained an adenoma in the descending colon; neither polyp had been detected on preoperative barium enema or at operation. A 58-year-old man underwent surgical polypectomy to remove a large villous adenoma in the descending colon that was discovered by colonoscopy 6 months after emergency right hemicolectomy for a Dukes' B carcinoma (without preoperative barium enema). The initial resection specimen had contained a 2-cm adenoma. Both patients remain well after 38 and 53 months respectively. No patient followed by clinical examination alone has presented with symptoms or signs of a missed synchronous lesion.

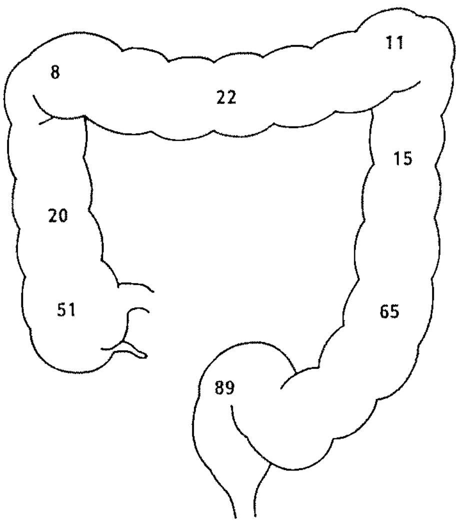

Figure 1 *Distribution of resected cancers*

Table 1 *Operations performed and prevalence of unsuspected synchronous adenoma and synchronous cancer within the resection specimen*

Primary operation	Total	Adenomas	Cancer
Abdominoperineal resection	23	7 (30)	0 (0)
Anterior resection	75	19 (25)	2 (3)
Sigmoid colectomy	48	9 (19)	1 (2)
Left hemicolectomy	28	4 (14)	0 (0)
Transverse colectomy	8	1 (12)	1 (12)
Extended right hemicolectomy	6	1 (17)	1 (17)
Right hemicolectomy	78	23 (29)	0 (0)
Subtotal colectomy	8	2 (25)	0 (0)
Proctocolectomy	1	1 (100)	0 (0)

Values in parentheses are percentages

Table 2 *Patients followed endoscopically and clinically within 2 years of surgery for colorectal cancer*

	Endoscopic ($n = 57$)	Clinical ($n = 185$)	*P*
Median age (years)	61	73	<0·001‡
Dukes' stage			
A	8 (14)	17 (9)	n.s.§
B	30 (53)	103 (56)	
C	18 (32)	65 (35)	
'D'	1 (2)	0 (0)	
Polyps*			
Adenoma	22 (39)	41 (22)	n.s.§
Metaplastic†	9 (16)	9 (5)	<0·05§

Values in parentheses are percentages. *Prevalence of synchronous polyps found either before surgery or in the resection specimen; †without adenoma. ‡Mann–Whitney *U* test; §χ^2 test; n.s., not significant

Table 3 *Patients screened endoscopically for metachronous colorectal cancer ≥2 years after surgery*

	First colonoscopy ($n = 28$)	Second colonoscopy ($n = 20$)	Total ($n = 48$)
Median age (years)	58	53	56
Cancer in left colon (distal to splenic flexure)	21	11	32
Dukes' stage			
A	2	2	4
B	19	10	29
C	7	7	14
'D'	0	1	1
Polyps in resection specimen			
Adenoma	5	6	11
Metaplastic*	2	3	5
Previous colonoscopy			
Adenoma	—	8	8
Metaplastic*	—	1	1

*Without adenoma

To date, 48 patients have undergone surveillance colonoscopy ≥2 years after initial surgery. This was a first examination for 28 patients; the other 20 had already undergone colonoscopy within 2 years of surgery, which confirmed that the colon was 'clean'. *Table 3* shows the characteristics of these patients. Twelve of 28 who had their initial colonoscopy >2 years after surgery have since had a second examination. Fourteen patients have had three or more colonoscopies.

Results of surveillance for metachronous tumours are shown in *Table 4*. Sixty colonoscopies were performed after the initial screening examination. Adenomas were detected and removed on 21 occasions (35 per cent). Three asymptomatic cancers were detected on follow-up colonoscopy, 4 years (one tumour) and 6 years (two) after the original resection. Two were early Dukes' A cancers while the third, although small, flat and

Table 4 *Repeated screening for metachronous colorectal cancer* ≥ 2 *years after surgery*

Colonoscopy	Total no. of patients	Patients with carcinoma	Patients with adenoma
First	20	0	5
Second	32	2	9
Third	14	0	7
Fourth	9	1	2
Fifth	5	0	3

Table 5 *Comparison of patients with normal and abnormal findings on colonoscopy*

	First colonoscopy		Second colonoscopy	
	Normal*	Abnormal	Normal*	Abnormal
No. of patients	66 (78)	19 (22)	21 (66)	11 (34)
Median age (years)	59	62	52	53
Cancer in left colon (distal to splenic flexure)	42 (64)	11 (58)	12 (57)	5 (45)
Dukes' stage				
A	8	2	3	0
B	36	13	12	7
C	21	4	5	4
'D'	1	0	1	0
Polyps in resection specimen				
Adenoma	12	10‡	6	5
Metaplastic†	8	3	0	2
Polyps on first colonoscopy				
Adenoma	—	—	5	7§
Metaplastic†	—	—	1	0

Values in parentheses are percentages. *Includes patients with local recurrence; †without adenoma. ‡$P < 0\cdot01$ (abnormal *versus* normal on first colonoscopy); §$P < 0\cdot05$ (abnormal *versus* normal on second colonoscopy); Fisher's exact test

apparently superficial, had metastasized to two local lymph nodes. Only one metachronous cancer was within reach of the 60-cm sigmoidoscope. All three patients had undergone colonoscopy previously, two within 2 years and one 5 years earlier.

One patient of those who had been followed clinically for >2 years after surgery without colonoscopy developed a symptomatic carcinoma. This 61-year-old man, who had undergone abdominoperineal resection for a Dukes' B carcinoma of the rectum 6 years previously, presented with altered bowel habit from a Dukes' B carcinoma of the caecum. The original resection specimen contained a single adenomatous polyp and the residual colon when resected contained five further adenomas showing moderate dysplasia. No symptomatic polyps were detected in this unscreened group.

Recurrent tumour

Local or anastomotic recurrence was detected by colonoscopy in only one patient, who underwent sigmoid colectomy 4 years previously. However, another patient developed intestinal obstruction resulting from extramural local recurrence involving the previous anastomosis; this had not been diagnosed at colonoscopy 4 months earlier. In contrast, eight patients developed local recurrence after anterior resection of the rectum that was diagnosed by rigid sigmoidoscopy. Three of these have undergone abdominoperineal resection and one is alive and well 5 years later.

Criteria for selection

Selective postoperative colonoscopy detected missed synchronous or metachronous adenomas at first examination in 19 patients (22 per cent of those examined) and metachronous cancer or adenoma at second or subsequent colonoscopy on 23 occasions (38 per cent of examinations). Patients who had an adenoma in the colon at first colonoscopy were more likely to have had one in the initial resection specimen ($P < 0\cdot01$) and more likely to develop further metachronous lesions ($P < 0\cdot05$). However, 47 per cent of patients with a postoperative adenoma did not have such a lesion in the resection specimen (*Table 5*).

Discussion

In this series the performance of barium enema for detecting synchronous lesions was poor, particularly when the second tumour was close to the index cancer. Other authors have reported similar findings. In the study of Maxfield[7] only five of 26 colonoscopically detected neoplasms (one of four cancers) were identified by barium enema, while Weber *et al.*[8] failed to detect by such enema any of three synchronous cancers and only five of 14 synchronous adenomas subsequently detected by colonoscopy. Colonoscopy is a more sensitive technique, especially for the detection of polyps <10 mm in diameter, although data from a survey of diagnostic colonoscopy in the USA suggest that the entire colon is visualized in only 75 per cent of patients[9]. Furthermore, Tate *et al.*[10] found that the rate of successful colonoscopy fell to 42 per cent in the presence of carcinoma. After operation, however, colonoscopy is a much easier and quicker procedure. In some cases a 60-cm endoscope will be sufficient to reach the ileum.

In the present study no missed synchronous cancer was found after surgery. Many adenomas remained, as demonstrated by the 25 per cent detection rate among those undergoing colonoscopy within 2 years of surgery. However, it can be argued that to miss some synchronous lesions during preoperative investigations may not always be important. Half will lie within the planned resection and the majority will be single adenomas <1 cm in diameter with a low malignant potential[11]. Most will not present a significant risk to the elderly patient or to those with a poor prognosis from an advanced tumour. Furthermore, it has been argued that most adenomas and some early cancers can be managed satisfactorily by postoperative colonoscopy[12]. It was unfortunate that two patients in the present series required reoperation to remove large synchronous adenomas that had been missed. However, since one patient required emergency surgery and the other had a stenosing lesion initially it is probable that both adenomas would have remained undetected even if preoperative colonoscopy had been performed.

Colonoscopy has also been recommended for the early detection of local recurrence[13]. Whereas endoscopic inspection of the anastomosis after anterior resection of the rectum is clearly important, colonoscopy has not been found to be useful for cancer of the more proximal colon. Although 10–15 per cent of recurrences involve the anastomosis[14], most begin in extraluminal tissues and invade the bowel secondarily[15].

It is well recognized that patients who survive resection for colorectal cancer are at risk of developing a second metachronous cancer; four patients who entered the present study had undergone resection many years earlier. The results of this surveillance programme confirm that many patients will continue to develop adenomas in the early years after surgery. To prevent progression to invasive carcinoma, several authors have recommended annual colonoscopy because they have detected metachronous adenoma[16] after median intervals as short as 18 months and metachronous cancer[17] within 24 months. In the present series, three patients developed metachronous cancer despite colonoscopic surveillance. The shortest interval between detection of metachronous cancer and previous colonoscopy was 18 months and on that occasion three other metachronous adenomas had been removed. It is possible that some apparently 'early' metachronous tumours may not have been detected at a previous endoscopic examination, while in other patients the interval between examinations may have been too long.

At the beginning of the series a few patients were not entered into the surveillance programme. One symptomatic metachronous cancer developed in a patient who would now have entered into the programme. Although this was a bulky Dukes' B cancer, the patient remains well 4 years after resection. Therefore, it still remains to be shown whether colonoscopic surveillance influences long-term survival.

It is probable that any survival advantage of postoperative colonoscopy will be demonstrated only by a controlled trial. Although Gilbertsen and Nelms[18] reported a decrease of 85 per cent in the expected incidence of invasive rectal carcinoma in more than 20 000 patients who underwent annual sigmoidoscopy, it is not known whether all patients with colorectal cancer would benefit similarly as the majority are >70 years of age or can be expected to die from recurrent disease. For these reasons patients in the present study were selected for colonoscopy primarily on the basis of relative youth and good prognosis.

Patients with an adenoma in the resection specimen commonly had a second polyp that could be removed at initial colonoscopy, and metachronous polyps were more likely to develop in those who had had at least one synchronous polyp. Similar findings were reported by Brahme *et al.*[19] and Bussey and colleagues[20], although Cullen *et al.*[21] failed to show such an association. However, we do not feel this should be used as the sole criterion for selection. Other studies suggest that more cancers develop in those who have a genetic predisposition to large bowel neoplasia[22]. Furthermore, patients with colorectal cancer who have an affected first-degree relative may be more likely to have synchronous tumours and develop metachronous lesions[23]. Fitzgibbons *et al.*[24] have shown this to be the case for hereditary non-polyposis colonic cancer and for this reason recommended subtotal colectomy. It is important, therefore, to obtain an adequate family history before surgery.

The results of the present study have encouraged continuation of a policy of selective postoperative colonoscopy. Those excluded have come to little harm and have been spared unnecessary examinations. However, it appears that the young patient with repeated metachronous polyp formation who has already survived 5 years from operation for the index cancer is at high risk for the development of metachronous cancer and may well require more aggressive follow-up.

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Increased risk of colorectal cancer associated with congenital anomalies of the urinary tract

Two young mothers of children presenting with congenital anomalies of the urinary tract underwent colectomy for carcinoma or adenomatosis of the colon. In another family with urinary anomalies, the maternal grandmother had died from carcinoma of the colon at 36 years of age. This previously unreported association led to two reviews. In the first, of 14 patients with colorectal cancer presenting under 45 years of age, three had known congenital urinary tract anomalies. In the second, which included the first three families, a detailed family history was obtained from children receiving treatment for congenital anomalies of the urinary tract. Seven of 116 grandparents and two mothers among 58 parents had colorectal carcinoma or adenomatosis of the colon; this was significantly greater than the expected incidence. A family history of congenital anomalies of the urinary tract may be a useful marker in screening for colorectal cancer.

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Carcinoma of the large bowel is the second most common form of cancer, causing about 20 000 deaths each year in the UK. Screening for colorectal cancer is expensive and involves testing for occult blood in the stool, with follow-up colonoscopy or barium enema for those with abnormal results. Recently the 'mutated in colorectal cancer' gene (*MCC*) has been isolated. This gene, which is found[1,2] on chromosome 5, is abnormal in cancers of the large bowel and thought to be a tumour suppressor that prevents cells from growing in the uncontrolled manner that characterizes cancer. There are other tumour markers that may be useful in deciding which families should be screened for colorectal cancer: osteoma of the mandible[3], skin tags[4] and congenital hypertrophy of the retinal pigment epithelium[5]. This preliminary paper reports an association of colorectal cancer with congenital anomalies of the urinary tract.

Patients

Initial patients

The association of congenital renal anomalies with colorectal cancer was first noticed in the family history of two patients who had a duplex pelvicalyceal collecting system and an ectopic ureterocele (*Figures 1* and 2). In the first family the mother underwent right hemicolectomy at the age of 31 years for carcinoma of the caecum; in the second the maternal grandmother had died at 36 years from carcinoma of the colon. More recently the mother of another patient with vesicoureteric reflux required total colectomy for multiple adenomatosis of the colon (*Figure 3*).

Patients under 45 years with colorectal cancer

Fourteen patients under the age of 45 years who presented with carcinoma of the large bowel were identified. Three of these patients had known urinary tract problems: pelvic ectopic kidney (one patient), duplication of the pelvicalyceal collecting system (one) and renal transplantation for chronic renal failure, possibly secondary to reflux nephropathy (one).

Investigated families

Twenty-nine consecutive families attending for follow-up of a congenital urological condition were studied. A detailed family history over three generations was taken from patients with a duplex pelvicalyceal collecting system (five families), vesicoureteric reflux (11), pelviureteric junction hydronephrosis (five) or ectopic ureterocele (eight). (As an ectopic ureterocele is associated with duplication, 13 families had a duplex system.) Findings in the 58 parents and 116 grandparents of these 29 families are shown in *Table 1*. Seven grandparents died from colorectal cancer at ages ranging from 36 to 84 years, of whom four were under 55 years of age. Other cancers were also found among the grandparents (stomach, four; oesophagus, two; melanoma, one; lung, one; uterus, one; leukaemia, one). Three grandparents also suffered from rheumatoid arthritis, which is related to human leucocyte antigen 27 and thus has a genetic basis. Three parents had received surgical treatment for malignant disease (carcinoma of the colon, one; multiple

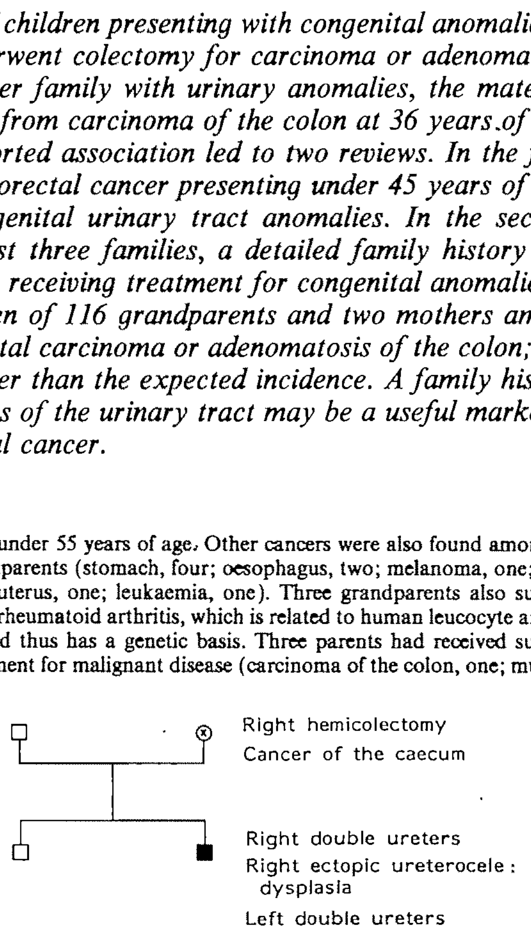

Figure 1 *Family history showing cancer of the colon in the mother of a patient with double ureters, ectopic ureterocele and dysplastic upper moiety of the affected kidney*

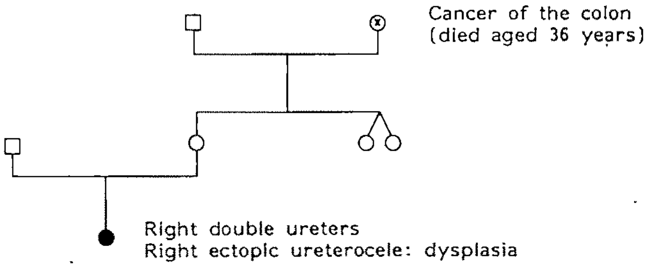

Figure 2 *Family history showing cancer of the colon in the maternal grandmother of a patient with double ureters, ectopic ureterocele and a dysplastic upper moiety of the affected kidney*

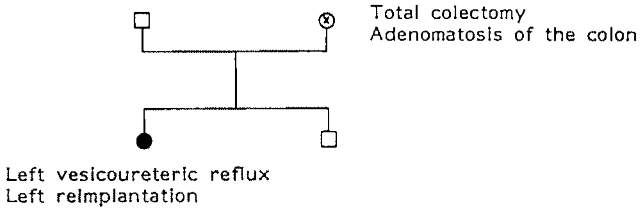

Figure 3 *Family history showing multiple colonic adenomatosis of the colon in the mother of a patient with vesicoureteric reflux*

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Table 1 *Cause of death and details of malignant disease in parents and grandparents of 29 families with congenital anomaly of the urinary tract*

	Affected grandparents		
Index families	Cause of death	Age (years)	Affected parents
Ectopic ureterocele ($n = 8$)	Cancer of the colon*	36	
	Cancer of the stomach	49	1 mother
	Cancer of the lung	78	Cancer of the colon at 33 years*
	Leukaemia	45	Alive and well
	Multiple sclerosis Rheumatoid arthritis	49	
Double ureters (with or without vesicoureteric reflux) ($n = 5$)	Cancer of the uterus	49	
	Cancer of the stomach	75	1 father
	Cancer of the stomach	56	Cancer of the testis at 30 years
	Cancer of the colon*	57	Alive and well
	Cancer of the colon*	49	
	Coronary	58	
Vesicoureteric reflux ($n = 11$)	Cancer of the colon*	48	
	Cancer of the colon*	61	1 mother
	Cancer of the stomach	40	Adenomatosis of the colon at 30 years*
	Leukaemia	45	Alive and well
	Melanoma of eye	50	
	Renal failure	64	
	Coronary	55	
	Rheumatoid arthritis Respiratory failure	58	
Pelviureteric junction hydronephrosis ($n = 5$)	Cancer of the rectum*	53	
	Cancer of the rectum*	84	
	Cancer of the oesophagus		
	Cancer of the oesophagus (alive and well)		
	Coronary thrombosis		
	Coronary thrombosis		
	Rheumatoid arthritis (alive and well)		
	Hypertension		
	Unknown		

*Colorectal neoplasia

Table 2 *Rates per 100 000 population of newly diagnosed cases of cancer*

Colorectal cancer	Age (years) 30–34	55–59	Total	Wessex standardized registration ratio
ICD 153				
M	1·1	36·1	26·7	1·13
F	1·6	37·8	31·1	1·16
ICD 154				
M	1·1	35·6	21·7	0·81
F	0·6	19·3	16·1	1·02

Data from the 1985 Office of Population Censuses and Surveys cancer registration statistics. ICD 153, colonic cancer; ICD 154, rectal cancer

adenomatosis of the colon, one; carcinoma of the testis, one). All the parents were alive and symptom-free.

Results

The incidence of colorectal cancer in the parents and grandparents was compared with that in the general population. Two assumptions were made: first, that the diseases were contained within ICD classifications 153 (cancer of the colon) and 154 (cancer of the rectum); second, that the age groups 30–34 years and 55–59 years were representative of the age distribution of the parents and grandparents respectively. A correction factor for Wessex was applied by the use of the standardized registration ratio (*Table 2*). Figures published by the Office of Population Censuses and Surveys for 1985 were used to calculate the expected number of cases of cancer in the 174 parents and grandparents in the families studied (*Table 3*). Many more cases were observed than would be expected, by a factor of 118 (99 per cent confidence interval 41–263).

Table 3 *Calculation of expected incidence of colorectal cancer for 174 observed parents and grandparents*

	Age (years) 30–34 ($n = 58$)	55–59 ($n = 116$)	Total ($n = 174$)
Observed cases of colorectal cancer	2	7	9
Expected nos			
ICD 153	0·0008	0·043	
ICD 154	0·0005	0·032	
Total	0·0013	0·075	0·076
Standardized incidence ratio (99% c.i.)	1538 (80–7134)	94 (27–229)	118 (41–263)

ICD 153, colonic cancer; ICD 154, rectal cancer; c.i., confidence interval

Discussion

Both genetic components[6,7] and environmental factors, such as dietary intake, are important in the aetiology of colorectal cancer. The chance of a given individual developing carcinoma of the large bowel probably depends on the interaction of these two elements. The stronger the genetic factor, the greater is the chance of developing the disease at an early age. Colorectal cancer is one such example: at one end of the spectrum is familial adenomatous polyposis with a malignant predisposition that is inherited as an autosomal dominant gene, while at the other is sporadic colorectal cancer, in which environmental factors appear to be of greater importance. Between these extremes lies hereditary non-polyposis colonic cancer[8]. The clinical features of these patients differ from those of patients with sporadic cancer in that they present earlier (average age 45 years), there is a predominance of neoplasms in the proximal colon (embryological midgut), the incidence of synchronous and metachronous tumours is higher, and only about 25 per cent of lesions are located in the sigmoid colon or rectum.

Adenomatous polyps are often found in association with colorectal cancer[8]. This relationship has been fully investigated in 34 kindreds comprising 670 individuals with either familial clusters of colorectal cancer or a single person with an adenomatous polyp[9]. The results suggested an inherited susceptibility to colonic adenomatous polyps and colorectal cancer with a gene frequency of 19 per cent. The authors suggested that mapping of a susceptible gene locus (or loci) would allow the genotype of individuals at risk to be determined. This is now a real possibility with the isolation of the *MCC* gene[1]. Such screening methods would be expensive and impractical for routine use at this stage. Screening for faecal occult blood is expensive and not rewarding[10]. Screening based on the findings from genetic counselling for relatives of patients with colorectal cancer[11] has a high rate of acceptance (90 per cent) and led to the finding of polyps in 62 of 382 high-risk patients and five with colonic cancer. Thus, identification of a genetic link with a readily identifiable congenital anomaly of the urinary tract has considerable positive implications for screening.

Ectopic ureterocele associated with double ureters, a duplex pelvicalyceal collecting system, vesicoureteric reflux and pelviureteric junction hydronephrosis are all known to have genetic factors in their aetiology and are often inter-related[12]. The results of the present study support the hypothesis that a family history of congenital urinary tract anomalies is associated with colorectal cancer and could be used as a phenotype marker, thus allowing screening of high-risk individuals. In this series other cancers affecting the gastrointestinal tract were also found, which suggests a possible relationship of congenital urinary tract anomalies with families prone to cancer[6,13]. In a national survey of the cancer family syndrome from Finland[13] covering 196 members of 22 kindreds, 120 (61 per cent) had colorectal cancer, 30 (15 per cent) unspecified intra-abdominal cancer, 20 (10 per cent) endometrial tumours, seven (4 per cent) gastric, five (3 per cent) biliary tract and 14 (7 per cent) other tumours. These data support an autosomal dominant inheritance for the transmission of colorectal cancer through two to four generations.

Although the findings in the present investigation are significant, they should be treated with caution because of the small numbers and the method of data collection; the results include the three families whose details suggested the association. The necessary assumptions made in the statistical comparison may also have affected the findings. Nevertheless, there is an apparent excess of colorectal cancer in the families of children with congenital anomalies of the urinary tract, a fact complemented by the high incidence of urinary anomalies in young patients with colorectal cancer. The incidence of pelvic ectopic kidney[14] is 1 in 800 and that of bifid or double ureters[14,15] approximately 1 in 140. Thus the high incidence found in the present study in 14 young patients with colorectal cancer represents a marked increase over the expected incidence of these two conditions. This supports the hypothesis that, in younger patients, genetic components are more important than dietary and other factors in the aetiology of colorectal cancer.

Hence, it would be wise when taking a history from a patient with colorectal cancer to enquire about any congenital urinary tract anomalies occurring in the family. Similarly, when taking a history from a patient with a congenital urinary tract anomaly, an enquiry into the coexistence of malignant disease in the family should be made. However, further studies are required to confirm or refute these associations.

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Endoscopic transanal resection in the management of patients with sessile rectal adenomas, anastomotic stricture and rectal cancer

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Forty patients underwent 61 endoscopic transanal resections using a urological resectoscope. Preoperative diagnoses were adenoma in 28 patients, carcinoma in seven and benign anastomotic stricture in five. Four patients with adenomas were found to have frank carcinoma. Ablation of 22 of 23 adenomas was achieved, 11 with a single transanal resection. Open operation was required for one patient. Locally advanced rectal malignancy was palliated in five of seven patients. All those with benign anastomotic stricture were cured by a single resection. The median operating time was 25 min, with 11 procedures exceeding 30 min. There were complications in seven cases (six bleeding, one septicaemia). The median hospital stay for the procedure alone was 3·5 days. There were no deaths within 30 days of operation. Endoscopic transanal resection is minimally invasive, quick, safe and effective. Histological surveillance is a major advantage and appears reliable. Low complication rates can be achieved by opting for several 'easy' resections and by restricting use of the procedure to lesions within 15 cm of the anal verge.

The management of benign lesions of the rectum is usually straightforward. Low lesions within comfortable reach of the examining finger can be removed by the open peranal route popularized by Parks[1]. Narrow-based polyps can be snared using an endoscope. Lesions above the peritoneal reflection too large for the snare can be removed at open operation. There remains a difficult group of lesions situated between these two sites where removal from below can become an imprecise and bloody procedure and open ablation may be associated with complications that are difficult to accept for benign disease. Because histological examination of any material removed is highly desirable, transanal resection using a urological resectoscope has been developed[2]. The method may also be used in the palliation of locally advanced rectal malignancy and in the cure of low anastomotic stricture.

Patients and methods

The procedure has been described previously[3]. The rectum is prepared by the administration of two rectal washouts on the evening before surgery. The operation is performed under standard inhalational general anaesthesia in the Trendelenburg lithotomy position. Antibacterial prophylaxis with metronidazole 500 mg and cefuroxime 750 mg is given intravenously at induction.

A standard 24-Fr urological resectoscope (Karl Storz Endoscopes, Rimmer Brothers, London, UK) with its 30° telescope is inserted through the anus using 1·5 per cent glycine solution as irrigant. An occlusive bung is not required. Resection is carried out using the loop-cutting electrode and cuttings are harvested for histology. Great care is taken not to breach the muscular wall of the rectum and, if significant difficulty is experienced from bleeding or tumour bulk, the procedure is terminated and the patient readmitted 6 weeks later for a further resection.

A 26-Fr Foley balloon catheter is inserted through the anus and inflated with 30–50 ml water to tamponade the resulting raw area and allow the escape of residual fluid. In women a 12-Fr urethral catheter is also inserted. Both are removed the following day. Patients are allowed home after the first bowel action, which usually occurs within 3 days.

In benign conditions, if the resection is judged incomplete the patient is readmitted for further endoscopic transanal resections at 6-week intervals until clearance is achieved. Subsequent follow-up consists of rigid or fibreoptic sigmoidoscopy; residual or recurrent nodules are fulgurated if small, otherwise a further transanal resection is arranged.

Results

Over a 4-year period, 61 procedures were performed on 40 patients. The results for the first 12 patients have been published[3] and are included in the present series.

Adenoma (Figure 1)

Twenty-eight patients (17 men, 11 women; median age 71 (range 39–86) years) with a preoperative diagnosis of benign adenoma of the rectum underwent 45 procedures. Eight patients presented with recurrence after other forms of treatment elsewhere: five had undergone peranal or snare polypectomy

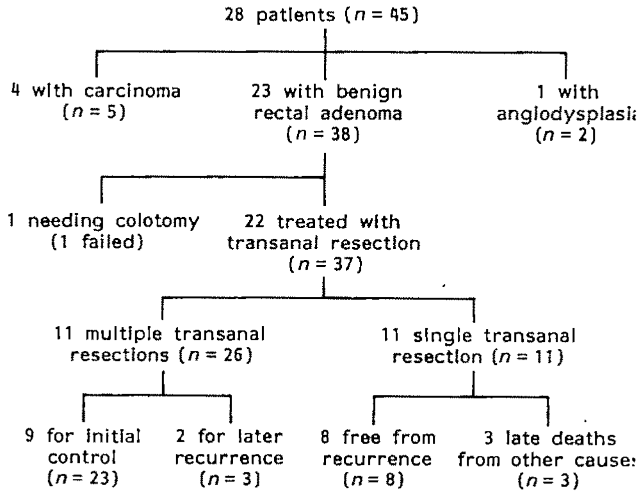
28 patients (n = 45)
4 with carcinoma (n = 5)
23 with benign rectal adenoma (n = 38)
1 with angiodysplasi (n = 2)
1 needing colotomy (1 failed)
22 treated with transanal resection (n = 37)
11 multiple transanal resections (n = 26)
11 single transanal resection (n = 11)
9 for initial control (n = 23)
2 for later recurrence (n = 3)
8 free from recurrence (n = 8)
3 late deaths from other cause: (n = 3)

Figure 1 *Management of patients with a preoperative diagnosis of rect adenoma. Values in parentheses are numbers of endoscopic transan resections*

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Table 1 *Patients found at transanal resection not to have benign adenoma*

Patient no.	Sex	Age (years)	Quadrants polypoid or sessile	Distance from anal verge (cm)	No. of transanal resections	Tissue diagnosis: Before transanal resection	Tissue diagnosis: After transanal resection	Outcome
1	M	70	3 sessile	6–10 (? upper limit)	2	Villous adenoma	Villous adenoma plus severe dysplasia	Anterior resection. Histological examination showed adenocarcinoma in an extensive villous adenoma with lymph node involvement. Later endoscopic transanal resection for anastomotic stricture
2	M	83	2 sessile	10	1	Tubular adenoma (? carcinoma)	Adenocarcinoma	Too frail for anterior resection. Palliation by endoscopic transanal resection. Died 2 months later
3	M	80	1 polypoid	4	1	Villous adenoma	Adenocarcinoma	Anterior resection
4	M	71	3 sessile	6–7	1	Villous adenoma	Adenocarcinoma	Abdominoperineal resection, radiotherapy
5	M	39	2 sessile	25	2	—	Angiodysplasia	No recurrence at colonoscopy 3 months after surgery

Table 2 *Patients with benign adenoma treated by a single transanal resection*

Patient no.	Sex	Age (years)	Quadrants polypoid or sessile	Distance from anal verge (cm)	Tissue diagnosis: Before transanal resection	Tissue diagnosis: After transanal resection	Resection time (min)*	Hospital stay (days)	Follow-up (months)	Outcome
6	M	55	1 polypoid	14	—	Villous adenoma	10	3	19	No recurrence
7	M	71	1 polypoid	3	—	Villous adenoma	20	4	6	Died after 6 months from synchronous Dukes' C carcinoma of the colon
8	F	81	3 sessile	9–15	—	Villous adenoma	45	5		Died from cerebrovascular accident after 2 months
9	F	75	1 polypoid	9	—	Tubular adenoma	30	4	4	No recurrence
10	F	75	1 polypoid	12	Tubular adenoma	Tubular adenoma	15	3	3	No recurrence
11	F	54	1 polypoid, 1 polypoid	8, 10	Tubular adenoma	Tubulovillous adenoma	20	3	19	No recurrence
12	M	86	2 sessile	12	—	Villous adenoma	30	5	5	No recurrence. Died from myocardial infarction
13	F	85	3 sessile	2–4	Villous adenoma	Tubular adenoma	30	5	6	No recurrence
14	F	55	1 sessile	4–9	Villous adenoma	Villous adenoma	30	4	3	No recurrence
15	M	66	2 sessile	9	Villous adenoma	Villous adenoma	30	3	3	No recurrence
16	M	60	2 sessile	9–12	Tubulovillous adenoma	Tubulovillous adenoma	35	3	2	Awaiting follow-up
17	F	74	1 polypoid	16	Villous adenoma	Villous adenoma	Failed			Too mobile for transanal resection. Required open colotomy

*Median resection time 30 min

Table 3 *Patients with benign adenoma treated by multiple transanal resections*

Patient no.	Sex	Age (years)*	Quadrants polypoid or sessile	Distance from anal verge (cm)	Tissue diagnosis: Before transanal resection	Tissue diagnosis: After transanal resection	No. of transanal resections	Resection times (min)†	Reason for multiple resections	Follow-up (months)	Outcome
18	M	86	4 sessile	12–16	Villous adenoma	Tubulovillous adenoma	3	30, 45, 50	Initial control	6	No recurrence
19	F	75	2 sessile	8	Villous adenoma	Villous adenoma	4	25, 25, 20, 20	True recurrence	42	Initial control required two transanal resections. Recurred after 9 and 25 months. Controlled by two further resections
20	F	80	2 sessile	9	Villous adenoma	Tubulovillous adenoma	3	40, 20, 15	Initial control	36	No recurrence
21	F	53	3 sessile	10	Tubular adenoma	Tubular adenoma	2	20, 20	Initial control		Lost to follow-up
22	M	85	2 sessile	12	Tubulovillous adenoma	Tubulovillous adenoma	2	45, 30	False recurrence	2	'Recurrent nodule', histologically granulation tissue
23	M	80	3 sessile	7	Villous adenoma	Villous adenoma	2	25, 25	Initial control	3	No recurrence
24	M	52	2 sessile	6	Villous adenoma	Tubulovillous adenoma	2	35, 20	True recurrence	14	Recurrent villous adenoma after 14 months treated by one transanal resection
25	M	72	3 sessile	12–15	Villous adenoma	Villous adenoma	2	45, 30	False recurrence	2	Nodule at 2 months, histologically scar tissue on further transanal resection
26	M	63	4 sessile	2–10	—	Villous adenoma	2	55, 15	Initial control	2	Residual nodule fulgurated at sigmoidoscopy
27	M	59	2 sessile	6–7	Tubulovillous adenoma	Tubulovillous adenoma	2	35, 20	Initial control	2	Residual nodule fulgurated at sigmoidoscopy
28	F	71	2 sessile	10	Tubulovillous adenoma	Tubulovillous adenoma	2	20, 20	Initial control	3	No recurrence,

*Median age 72 years; †median resection time 25 min

Table 4 *Patients with advanced malignant disease treated by transanal resection*

Patient no.	Sex	Age (years)	Location of tumour	Symptoms	Distance from anal verge (cm)	Quadrants	No. of transanal resections	Outcome
29	F	89	Rectum	Bleeding, abdominal pain	9	4	1	Palliated
30	M	84	Rectum	Bleeding	3	2	2	Palliated
31	M	77	Rectum	Bleeding, incontinence	2	4	2 + 1 failed	Palliated for 3 months. Left iliac fossa colostomy for obstruction
32	F	85	Rectum	Bleeding	4–6	1	1	Palliated
33	F	46	Rectum	Bleeding, discharge, pelvic pain	3	3	1	Palliated. Operative bleeding required 2-unit transfusion
34	M	74	Prostate	Painful defaecation, rectal discharge	4	4	1	Not palliated. Left iliac fossa colostomy
35	F	80	Rectum	Incontinence	5	4	1	Not palliated

Table 5 *Patients with anastomotic stricture treated by transanal resection*

Patient no.	Sex	Age (years)	History	Distance from anal verge (cm)	No. of transanal resections	Resection time (min)	Follow-up (months)	Outcome
36	M	76	Stricture at 5 months after anterior resection for Dukes' C cancer of the sigmoid	5	1 + 1 (equipment failure)	15	None	Died after 9 months
37	M	70	Stricture at 9 months after reversal of Hartmann's operation for perforated cancer of the rectosigmoid, stapled anastomosis; failed dilatation	12	1	10	48	Cured. Died after 4 years from advanced metastatic disease
38	F	43	Stricture at 1 month after anterior resection for Dukes' B cancer of the rectosigmoid; failed dilatation	8	1	5	32	Cured
39	M	70	Stricture at 3 months after anterior resection for Dukes' C cancer of the rectum; stapled anastomosis	4	1	5	20	Cured, allowing closure of defunctioning colostomy 5 months after transanal resection
40	M	51	Stricture at 20 months after reversal of Hartmann's operation for Dukes' B cancer of the rectosigmoid; stapled anastomosis	8	1	25	3	Cured

and three anterior resection, two for carcinoma and one for an extensive villous adenoma with malignant degeneration. A preoperative tissue diagnosis of benign adenoma with varying degrees of dysplasia was obtained for 21 patients; in the remainder, endoscopic transanal resection was the method of biopsy and ablation. The initial diagnosis was revised in five patients as a result of transanal resection (*Table 1*). Three went on to anterior or abdominoperineal resection for malignant degeneration in villous adenoma. One patient with overt carcinoma was too frail for major surgery but underwent successful palliation by endoscopic transanal resection. The last patient, with bleeding from angiodysplasia, was successfully treated by transanal resection.

Table 2 summarizes the results for 12 patients (five men, seven women; median age 71 (range 54–86) years) with benign adenoma who underwent a single endoscopic transanal resection, and *Table 3* the results for 11 who required multiple transanal resections.

The degree of bleeding at operation was recorded as 'minimal' (34 procedures), 'moderate' (two) or 'severe' (one). In two procedures described as having minimal bleeding there was a significant drop in haemoglobin level (from 14·2 to 10·8 g/dl and from 14·0 to 10·0 g/dl). For the remainder the median change in haemoglobin level by the second day after operation was −0·9 (range −1·5 to 0·6) g/dl. The median time to the first bowel action was 3 days and the median hospital stay 4 days. The median follow-up to date is 4·5 (range 2–42) months; one patient has been lost. Seven patients were thought to have recurrence. Five were readmitted for endoscopic transanal resection whereupon two were shown histologically to have friable scar tissue; a further two required sigmoidoscopic fulguration for small nodules, the histology of which cannot be determined.

Carcinoma

Seven patients (three men, four women; median age 80 (range 46–89) years) underwent ten procedures for palliation of malignant disease (*Table 4*). Palliation was judged successful for rectal bleeding and impending obstruction but not for incontinence caused by rectal rigidity or pain from pelvic infiltration.

Operative difficulty resulted from narrowing of the lumen by the tumour, thereby impeding the passage of the resectoscope (two procedures), or bleeding (one). One procedure was abandoned when regrowth obliterated the lumen 3 months after successful palliation by transanal resection.

Two patients required multiple procedures: in each case two endoscopic transanal resections were necessary to control rectal bleeding. One patient required postoperative transfusion of 2 units. However, the mean drop in haemoglobin level was 0·6 g/dl. There were no other complications. The predicted median hospital stay for the procedure alone would have been 4 (range 3–6) days. Delay in discharge in two patients was due to fashioning of a defunctioning colostomy (21 and 33 days), and in a further two to social circumstances and referral for terminal care (10 and 11 days). No stay was prolonged because of complications of transanal resection.

All seven patients died from malignancy between 2 and 12 months after the last procedure.

Anastomotic stricture

Five patients (four men, one woman; median age 70 (range

43–76) years) underwent six procedures for anastomotic stricture following low colorectal anastomosis (*Table 5*) with failure of conventional dilatation in two cases. One operation failed after an equipment malfunction. Bleeding was recorded in all procedures as minimal. The median resection time was 10 (range 5–25) min. Histological examination of the resected tissue showed no evidence of tumour recurrence.

There were no complications. The median hospital stay, and time to bowel opening, was 3 (range 3–5) days. Four patients have complete resolution of symptoms and a wide patent anastomosis on endoscopy at a median follow-up of 26 (range 3–48) months. The fifth was lost to hospital follow-up but was reported to have died from advanced malignant disease 9 months after the procedure without return of symptoms.

Complications

Seven procedures were associated with complications. Bleeding was seen after six endoscopic transanal resections, generally for extensive or malignant lesions, in one case complicated by disseminated intravascular coagulation. Hypotension was seen in two of these events. One patient developed *Escherichia coli* septicaemia when antibacterial prophylaxis was omitted. No clinical or biochemical evidence of haemodilution was seen. There were no deaths within 30 days of any procedure.

The median operating time for the series was 25 (range 5–55) min, with 11 procedures exceeding 30 min.

Discussion

Endoscopic transanal resection allows the definitive treatment of sessile or broad-based polypoid adenomas of the rectum that are either too far from the anal verge for peranal resection or too extensive for snare polypectomy. The procedure spares patients radical surgery with its attendant risks.

Sessile adenomas of the rectum have considerable malignant potential. Fisher and Castro[4] examined 150–200 sections from four villous papillomas and found malignant change in three. With endoscopic transanal resection the polyp is resected piecemeal but histological assessment nevertheless appears adequate; no case labelled as 'benign' in the present study has subsequently manifested an unsuspected carcinoma during follow-up of up to 42 months.

Endoscopic transanal resection was combined with peranal resection on three occasions. The excellent view obtained with the resectoscope allowed a check of the fringes of the resected area for residual tumour and accurate haemostasis. An estimate of clearance was recorded at the time of operation for 36 procedures and was incorrect on four occasions, two positive and two negative. It appears from this and other series[5] that the most distal extent from which lesions can or should be resected is 15 cm from the anal verge; mobility of the colon above this level makes the procedure difficult and the risks of free intraperitoneal perforation are great.

Large sessile adenomas and malignant lesions can be highly vascular and difficult to resect. The operator should be prepared to curtail such resections and accept the need for multiple procedures; subsequent resections are easier as tumour bulk diminishes. This conservative policy may have been responsible for the low morbidity rate (11 per cent), a value that compares favourably with those in other studies[5,6]. Bleeding was the most common complication. Disseminated intravascular coagulation can occur and one episode of septicaemia occurred early in the present series. The use of intravenous peroperative antibacterial prophylaxis is mandatory. No biochemical or clinical evidence of haemodilution was seen. During this study the volume of irrigant was not measured; a prospective study is now under way in which the volumes of glycine used are between 3 and 6 litres per resection.

Follow-up endoscopy shows that endoscopic resection leaves an easily observed smooth scar that is slightly whiter than the normal rectal mucosa and causes no apparent functional impairment, even after an extensive resection.

It is difficult to give an exact figure for recurrence in this series; five patients underwent further endoscopic transanal resections for suspicious nodules, of which two proved to be scar tissue. The longest interval between initial control and true recurrence was 25 months and, as with transitional cell carcinoma of the bladder, the surgeon must accept the need for long-term surveillance.

There are now sufficient published data[7–9] to justify the use of endoscopic transanal resection in the palliation of a proportion of patients with advanced malignant rectal disease. Endoscopic resection palliated symptoms caused by intraluminal tumour bulk such as bleeding, tenesmus, discharge and impending obstruction but incontinence due to rectal rigidity was not helped in the one patient in this series; others[5] have noted some improvement.

Endoscopic transanal resection can be used only when the lumen is of sufficient size to allow passage of the resectoscope to the cephalad border[10–12]. One patient returned 3 months after successful palliation by transanal resection with a recurrence of bleeding and impending obstruction. Further endoscopic resection was impossible because of obliteration of the lumen and a defunctioning colostomy had to be fashioned. Routine follow-up sigmoidoscopy should be carried out in such cases. Despite the advanced age of most of the present patients, the procedure was well tolerated and, where there are reservations about general anaesthesia, the resection can be performed under light sedation[7].

The management of anastomotic stricture with this technique is unique to this series, although electrocoagulation has been used[13]. Unlike bougienage or balloon dilatation no force is required and histological specimens are available to exclude anastomotic tumour recurrence. The stricture is resected flush with the luminal wall and, because it is relatively avascular, bleeding is minimal. Staples were used for three of the five anastomoses but caused no problems with the electroresection.

The technique of transanal resection has a limited but valuable place in colorectal surgery. Discussion and liaison with colleagues over the past 3 years suggest that experience is needed for success and endoscopic resection is not a procedure for the occasional operator.

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Paper accepted 14 November 1992

Announcement

Eurosurgery '93

The 3rd European Congress of Surgery under the auspices of Eurosurgery will take place in London from 14 to 17 September 1993. This international congress embraces all the specialties within surgery and sessions will be sponsored by all of the surgical specialist associations and societies of the participating nations, ensuring that there will be an international and multidisciplinary approach to many common surgical problems. Additionally, there will be European symposia of general interest to all surgeons on themes such as endoscopy, management of patients with trauma, daycase surgery, graduated patient care, surgical audit and surgery in the developing world. A major session on surgical training is also being organized by the surgical trainees' associations.

A large number of free papers will also be given and these communications will be published in a special supplement of *The British Journal of Surgery*.

On 14 September 1993 a number of satellite sessions sponsored by companies are being organized for delegates.

Further details and registration forms may be obtained from the Congress Secretariat, Eurosurgery 1993, Conference Associates and Services Ltd, Congress House, 55 New Cavendish Street, London W1M 8RE, UK. Telephone: 071 436 0531. Facsimile: 071 935 7559.

J. P. S. Lumley

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Randomized trial comparing three forms of pelvic floor repair for neuropathic faecal incontinence

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A randomized controlled trial in women with neuropathic faecal incontinence compared total pelvic floor repair (n = *12) with anterior levatorplasty and sphincter plication alone* (n = *12) and postanal repair alone* (n = *12). Review at 6 and 24 months indicated that results were significantly better for total pelvic floor repair than either of the other procedures. Complete continence was achieved in eight of the 12 patients 2 years after total pelvic floor repair. Only total repair significantly elongated the anal canal. Both total pelvic floor repair and anterior levatorplasty improved sensation in the upper anal canal.*

Normal continence was once thought to be achieved by the flap-valve mechanism created by the anorectal angle[1,2]. Restoration of this angle by postanal repair was therefore proposed as the standard surgical treatment for neuropathic faecal incontinence[2,3]. However, recent studies have questioned the presence of a flap-valve mechanism[4,5] and have failed to detect any alteration in the anorectal angle after postanal repair. Furthermore, neuropathic faecal incontinence is not always associated with an obtuse anorectal angle[6–8]. Miller *et al.*[9] studied anterior levatorplasty combined with external sphincter plication as an alternative treatment for neuropathic faecal incontinence. The results of anterior levatorplasty were not significantly different from those of postanal repair. As the outcome after postanal repair is poor, the present authors have explored the role of total pelvic floor repair (combined postanal repair and anterior levatorplasty with external anal sphincter plication) for neuropathic faecal incontinence. Early results of this procedure in a non-randomized study were encouraging[10].

This report describes the results of a randomized trial comparing postanal repair, anterior levatorplasty and total pelvic floor repair for neuropathic faecal incontinence. The functional outcome and changes in physiological parameters are presented.

Patients and methods

Thirty-six consecutive women, aged 28–75 (median 51) years, were studied. All patients had neuropathic faecal incontinence confirmed by anorectal manometry, videoproctography and electromyography. Any patient with an isolated anal sphincter defect was excluded. The operative procedure was chosen from computer-generated random tables, each operation being performed on 12 patients. There was no significant difference in age or duration of incontinence between the three groups. All patients were incontinent to solid stool at least four times a month and each wore a pad. Twenty-seven patients were excluded because they had an isolated sphincter defect or coexistent pathology such as diabetes mellitus.

Anorectal manometry, anal canal sensation and videoproctography were performed before and 3 months after surgery. Electromyography was not repeated after operation because the patients withheld consent. The quality of continence 6 months after operation was assessed by the ability to control solid or liquid stool, anorectal awareness and the capacity to defer defaecation. These data were assessed using a scoring system (*Table 1*). The effects of surgery on continence, employment and the patient's sexual and social life were evaluated by a questionnaire 24 months after operation; comparisons between preoperative and postoperative status were made by means of a visual analogue scale (*Figure 1a*). Data from this questionnaire were plotted graphically (*Figure 1b*).

Controls. Eighteen female volunteers recruited from clinical staff and patients undergoing herniorrhaphy or cholecystectomy served as controls. None of these had previous anorectal complaints. Anorectal manometry was performed on all and videoproctography on 12.

Anorectal physiology

Anal manometry and assessments of rectoanal inhibitory reflex were performed using a closed water-filled balloon probe connected to a pressure transducer and Multi-Trace 4 multichannel recorder (Lectromed, Jersey, UK) as previously described[8]. Maximum basal pressure was recorded as the highest pressure at rest, whereas maximum squeeze pressure was the highest recorded pressure on voluntary contraction. Reduction of basal pressure by more than 10 per cent during balloon distension of the rectum was considered a normal rectoanal inhibitory reflex.

Sensation in the upper, mid and lower anal canal was measured with a unipolar probe generating a constant electrical stimulus ranging from 0 to 50 mA at a frequency of 20 Hz and a pulse of 0·3 ms.

Videoproctography was performed as previously described[11]; measurements included anal canal length, anorectal angle and funnel deformity at rest. Pelvic floor movement was measured during maximal squeeze and the presence of a rectocele sought during straining.

Electromyography was performed with a 0·64-mm diameter, 77-mm long concentric needle (Teka, Pleasantville, New York, USA) and a Medelec MS 91 machine (Medelec, Woking, UK). Motor unit potentials were analysed at rest, recruitment on squeeze and degree of inhibition on straining. Motor unit potentials were analysed separately for number of phases, amplitude and duration as described[12].

Surgical technique

All patients received a phosphate enema for bowel preparation and single-dose antibiotic prophylaxis with cefuroxime and metronidazole.

Postanal repair was performed as previously described[3] in the lithotomy position, although Prolene (Ethicon, Edinburgh, UK) was used for the repair. Anterior levatorplasty and sphincter plication was performed through a transverse incision midway between the vagina and anus and developed proximally as far as the peritoneal reflection, so that both limbs of the puborectalis were displayed on either side of the anorectum. The external anal sphincter was dissected off the internal sphincter and a nylon tape passed around it. Three or four Prolene sutures were used to approximate the levator ani muscles across the midline, care being taken to prevent inadvertent suture placement into

Table 1 *Scoring system for quality of continence*

Score	Incontinence to solids	Incontinence to liquid	Soiling	Other
1	None	None	None	No urgency
2	None	None	None	Urgency
3	<1 per month	Occasional	Minor	
4	>1 per month to <1 per week	Frequent	Major	
5	>1 per week but not daily			
6	Daily			Aware of defaecation
7	Daily			Unaware of defaecation

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1a When you pass stool do you have any warning?
1b Can you distinguish between gas and solid stool?
2/3/4a How frequently are you incontinent to gas/liquid/solids?
2/3/4b How much gas/liquid/solid do you leak?
2/3/4c How bad is the problem of gaseous/liquid/solid leakage?
2/3/4d Does flatus/liquid/solid incontinence interfere with your social life?
2/3/4e Does flatus/liquid/solid incontinence interfere with your employment?
2/3/4f Does flatus/liquid/solid incontinence interfere with your sexual relations?

Scale: 0 ____ 10
Best score Worst possible score

a

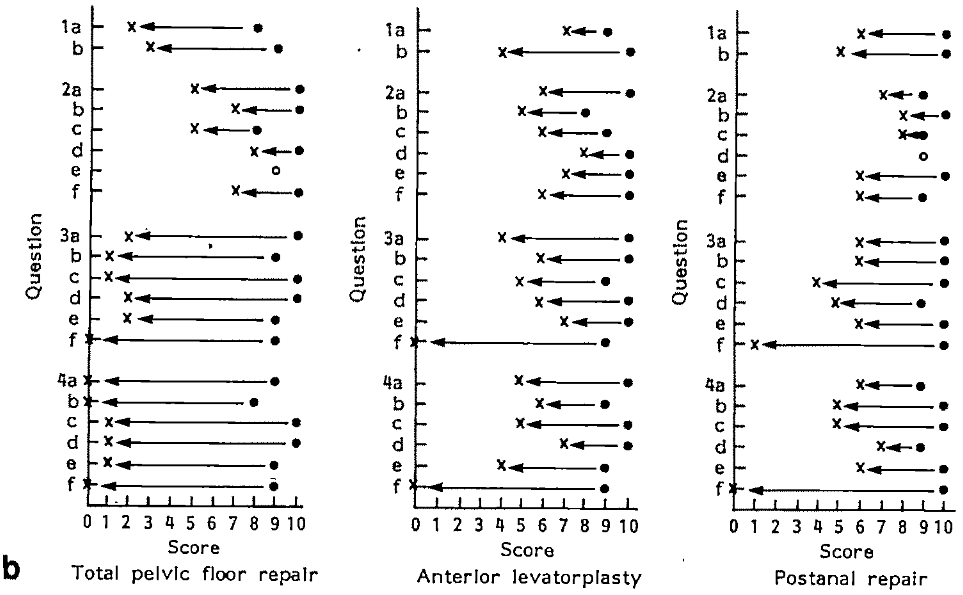

Figure 1 a *Linear analogue scale to assess extent of faecal incontinence. Questions refer to: 1, sensation; 2, flatus; 3, liquid stool; 4, solid stool.* b *Visual analogue comparison of preoperative* (●) *and postoperative* (x) *continence after total pelvic floor repair, anterior levatorplasty and postanal repair.* o, *No change*

the posterior vaginal wall. The external sphincter was plicated with Prolene sutures.

Statistical analysis

Paired and non-paired Student's *t* tests were used for comparison of sphincter pressures and videoproctographic parameters, as the data were shown to be normally distributed. Functional outcome was assessed by the Wilcoxon signed rank and Fisher's exact tests.

All patients and controls gave informed consent. The study was approved by the research ethical committee of the Central Birmingham Health Authority.

Table 2 *Complete continence to solid and liquid stool*

Procedure	No. of patients	Time after operation	
		6 months	2 years
Total pelvic floor repair	12	9	8
Anterior levatorplasty	12	4	4
Postanal repair	12	4	5

Results

Clinical

In one patient, the anterior wall of the anorectum was inadvertently opened during dissection of the rectovaginal space. The defect was closed endoanally without faecal diversion and the patient made an uneventful recovery. One wound infection was recorded. There was no significant difference in mean hospital stay between the groups (6 days in each).

Complete continence was achieved at 6 months, by nine patients after total pelvic floor repair, four after levatorplasty and four after postanal repair. These patients were aware of impending defaecation, could defer defaecation and were continent to solid and liquid stool ($P = 0{\cdot}02$, postanal repair *versus* total pelvic floor repair; $P = 0{\cdot}05$, anterior levatorplasty *versus* total repair – Fisher's exact test). However, all patients continued to wear pads at this stage of the assessment (*Table 2*).

Longer follow-up was achieved in all patients between 22 and 28 months after operation (median values: postanal repair, 24 months; levatorplasty, 22 months; total pelvic floor repair, 28 months). Two patients undergoing total pelvic floor repair deteriorated after the initial 6-month review but one improved after the first assessment; hence eight were completely continent to solid and liquid stool at 28 months. None wore a pad. Of the remaining four patients, two were continent to solids but experienced some soiling, necessitating use of a pad when the stool was liquid. Two patients were not improved. Changes in the continence score are shown in *Figure 2*.

In patients undergoing anterior levatorplasty, no further improvement was seen after the 6-month assessment. Four patients (two continuing to wear a pad) remained continent to solid and liquid stool. Eight others who were not improved later underwent postanal repair to complete the total pelvic floor repair. Following secondary total repair, four patients had improved anorectal function not requiring a pad and became continent to solid and liquid stool. Changes in the continence score are shown in *Figure 2*.

Of patients treated by postanal repair, a further patient

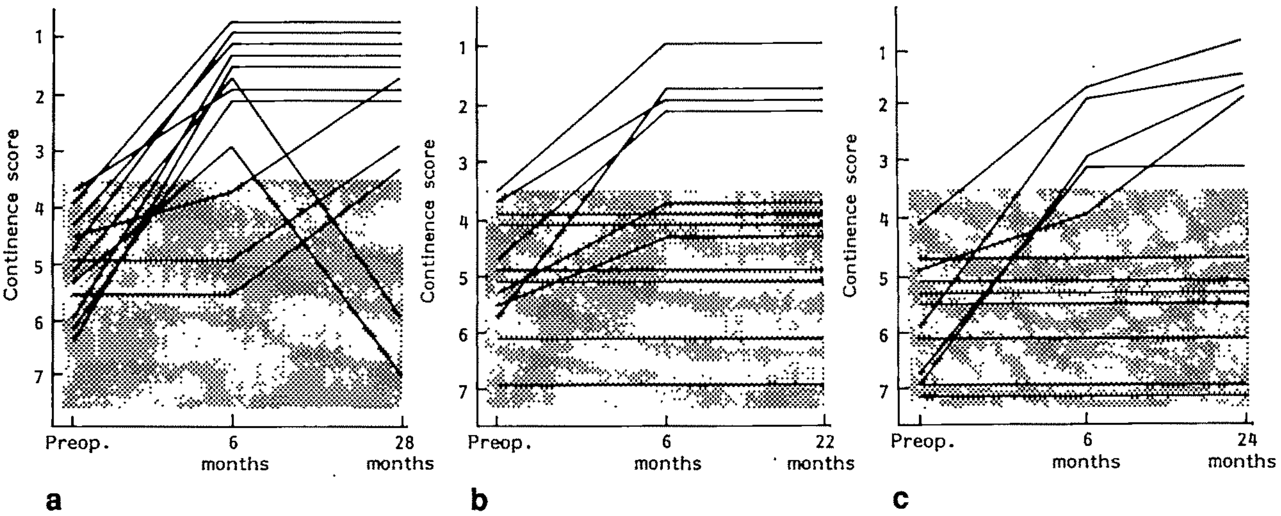

Figure 2 *Postoperative changes in continence score for* **a** *total pelvic floor repair,* **b** *anterior levatorplasty and* **c** *postanal repair.* ▨, *Unacceptable function*

Table 3 *Comparison of physiological parameters between all patients before and after operation and normal controls*

	Total pelvic floor repair		Anterior levatorplasty		Postanal repair		
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Controls
Manometry							
Mean(s.e.m.) maximum resting pressure (cmH_2O)	74(9)†	85(7)	70(9)‡	74(7)‡	73(11)†	84(9)	103(6)
Mean(s.e.m.) maximum squeeze pressure (cmH_2O)	136(15)‡	131(10)‡	121(15)‡	141(17)‡	132(17)‡	123(10)‡	211(13)
Rectoanal inhibitory reflex present	11 of 12	12 of 12	8 of 12†	10 of 12	11 of 12	11 of 12	18 of 18
Radiology							
Mean(s.e.m.) anal canal length (cm)							
Rest	3·2(0·4)	4·7(0·6)*	3·3(0·2)	3·9(0·5)	2·9(0·4)	3·1(0·3)	3·9(0·3)
Squeeze	4·0(0·4)	5·2(0·6)	3·6(0·3)†	4·2(0·5)	3·2(0·4)‡	3·5(0·4)†	4·6(0·3)
Funnel	8 of 12‡	6 of 12‡	9 of 12‡	8 of 12‡	10 of 12‡	8 of 12‡	0 of 12
Rectocele	11 of 12	7 of 12*	10 of 12	5 of 12	10 of 12	6 of 12	0 of 12
Mean(s.e.m.) pelvic floor movement (cm)							
Ascent	1·0(0·2)	0·4(0·1)*	0·2(0·1)†	0·5(0·2)	0·2(0·1)†	0·5(0·2)	0·8(0·2)
Descent	1·8(0·4)	2·5(0·6)	2·1(0·5)	1·9(0·3)	1·4(0·2)	1·3(0·5)	2·5(0·5)

* $P < 0·05$ *versus* preoperative; † $P < 0·05$ *versus* controls; ‡ $P < 0·01$ *versus* controls (Student's *t* test)

improved 10 months after operation, resulting in five who were continent to solid and liquid stool (*Table 2, Figure 2*).

From the visual analogue score it was evident that only total pelvic floor repair reduced the frequency and quantity of faecal leakage and improved the patient's social life and employment (responses 3 and 4; *Figure 1b*). Of sixteen patients who were sexually active before surgery, improved postoperative function resulted in all but one and was independent of the type of procedure. Five patients after anterior levatorplasty and five after total pelvic floor repair complained of dyspareunia following surgery. This is believed to relate to suture placement adjacent to the vagina and requires further evaluation. Unfortunately, none of the operations appeared to have a significant impact on continence to flatus, which was still a considerable problem in many patients (response 2, *Figure 1b*).

The median (range) frequency of faecal incontinence per month 2 years after postanal repair was 10 (0–30), after levatorplasty 5 (0–30) and after total pelvic floor repair 2 (0–12). Total repair was significantly better than postanal repair and levatorplasty ($P < 0·01$, Wilcoxon signed rank test).

Anorectal physiology

Although maximum resting and squeeze pressures were significantly lower in patients than in controls (mean maximum resting pressure 72 *versus* 103 cmH_2O, $P < 0·01$; mean maximum squeeze pressure 129 *versus* 211 cmH_2O, $P < 0·01$), none of the operations influenced these pressures significantly (*Table 3*).

The rectoanal inhibitory reflex was restored in the one patient after total pelvic floor repair, two of four patients after anterior levatorplasty and not in the one after postanal repair. All patients in whom this reflex was restored experienced an improvement in function. The most likely explanation for restoration of the rectoanal inhibitory reflex is an increase in the basal pressure recordings in the anal canal above 30 cmH_2O. The remaining three patients in whom no demonstrable reflex was seen continued to exhibit low basal pressures (20, 20 and 30 cmH_2O). Functional improvement in these three patients was unsatisfactory.

Radiology

The length of the anal canal at rest, as assessed by proctography, was significantly increased only after total pelvic floor repair (mean 3·2 *versus* 4·7 cm, $P < 0·05$). Neither anterior levatorplasty nor postanal repair influenced anal canal length significantly (*Table 3*). Movements of the pelvic floor were significantly reduced ($P < 0·05$) in patients undergoing total repair; the operation appeared to fix the pelvic floor at a lower position.

A funnel deformity associated with mucosal prolapse was common in incontinent patients and invariably absent in controls; however, this deformity was not corrected by any of the three methods of repair.

Upper anal canal sensation (0–12 mA) was impaired in nine patients before postanal repair, seven before levatorplasty and ten before total repair. All patients undergoing total pelvic floor repair and anterior levatorplasty and seven receiving postanal repair regained sensation in the upper anal canal.

Audit of total pelvic floor repair

Because the number of patients in this randomized study is small, all patients who have had a total pelvic floor repair using this technique who have been followed ⩾2 years were analysed. Of the 28 patients who have had a total pelvic floor repair, 25 are completely continent to liquid and solid stool.

Discussion

When postanal repair was first developed by Parks[2] as a treatment for neuropathic faecal incontinence, it was expected that the operation would restore the anorectal angle and thus the flap-valve mechanism. However, the rôle of the flap-valve mechanism in continence has since been questioned[4,5]. Furthermore, recent studies have revealed that the anorectal angle is not influenced by postanal repair[6–8] and that some patients with neuropathic faecal incontinence have a normal anorectal angle[7].

Following encouraging results in its early years[2,3], postanal repair was established as the standard operation for neuropathic faecal incontinence. However, its success in restoring continence to both solids and liquids varies from 13 to 88 per cent[6–8,13–15]. Early encouraging results from the present authors were not confirmed when patients were followed for a longer time[13]. This may have been because subjective improvement was discounted in a more critical evaluation by an unbiased observer. After reporting that 76 per cent of patients who underwent postanal repair still leaked faeces, the authors felt a need to develop a more effective operation. Furthermore, videoproctography frequently revealed that a rectocele, indicating an anterior pelvic floor deficiency, was often present in patients with neuropathic faecal incontinence.

Since 1987, a combined procedure (postanal repair and anterior levatorplasty), termed total pelvic floor repair[10], has been developed to reconstruct the entire pelvic floor. Early experience was that this procedure successfully restored continence to both solids and liquids in 55 per cent of 22 non-randomized patients[10]. These results were better than those of postanal repair performed in the previous decade but non-absorbable suture material was used for total pelvic floor repair compared with absorbable suture for the postanal operation. It was therefore decided to compare the effects of postanal and total pelvic floor repair in a randomized trial. However, because secondary total repair (addition of anterior levatorplasty after unsuccessful postanal repair) was also successful in 44 per cent of 14 patients[10], and because of the reported successful outcome of anterior repair[9], it was thought that primary levatorplasty alone might have a role in the treatment of neuropathic faecal incontinence. Therefore three groups were included in the trial: postanal repair, anterior levatorplasty and total pelvic floor repair.

The results of this trial have clearly shown that functional outcome after total pelvic floor repair is significantly better than after postanal repair or anterior levatorplasty alone. This is true both in the short and medium term. However, it is of interest that, after total repair, two patients deteriorated despite initial improvement. Deterioration in functional results was also observed after postanal repair, so it was felt important that patients in this study should be followed for at least 2 years.

Total pelvic floor repair was the only operation that elongated the anal canal significantly; it is believed that this explains, at least in part, the improvement in continence. Postanal repair had no significant effect on any physiological parameter, a result that almost completely reproduces previous findings[8]. Both total pelvic floor repair and levatorplasty improved sensation in the upper anal canal, which may have contributed to the improvement in continence after operation.

Impaired evacuation of faeces in association with neuropathic faecal incontinence is an important symptom that requires careful preoperative evaluation, particularly if there is a history of straining. This group of patients is at risk of worsening pudendal neuropathy after operation from straining at defaecation. In some patients, total pelvic floor repair was associated with impaired rectal evacuation in the early months after operation. A rectocele is another cause of impaired evacuation; this condition is usually considerably improved by both anterior levatorplasty and total repair, which reconstitute an anterior buttress. If patients have impaired rectal evacuation demonstrated during preoperative videoproctography without a rectocele or rectal intussusception, total pelvic floor repair is generally not recommended as this may further impair the evacuation of faeces.

It is recognized that the number of patients included in the trial is small, but 27 patients were excluded because they were men, because there was a defect in the sphincter or because of other coexisting pathology such as rectal prolapse, diabetes or a neurological disorder. Recruitment took 2 years and it became increasingly difficult to justify inclusion of more patients for treatment by postanal repair or levatorplasty alone when interim results at 6 months suggested a significant advantage with total repair[16].

Total pelvic floor repair is a new operation. The early results are encouraging and at this stage the outcome in women with neuropathic faecal incontinence is better than following anterior levatorplasty or postanal repair. However, total pelvic floor repair is not appropriate for patients with an isolated sphincter defect, which may be amenable to sphincter repair alone. Also, total repair is not advised in those without an intussusception or rectocele who have unexplained impairment of evacuation. Although the present trial suggests that total pelvic floor repair is the optimum form of repair for the majority of women with neuropathic faecal incontinence, further evaluation of larger numbers of patients is required. Nevertheless, a prospective audit in 28 patients followed for ⩾2 years has revealed that continence to liquids and solids was restored in 89 per cent. These observations support the belief that total pelvic floor repair is the optimum procedure for neuropathic faecal incontinence.

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Paper accepted 6 November 1992

Announcement

Surgery of the Liver, Biliary System and Pancreas

The British Council are holding a course devoted to Surgery of the Liver, Biliary System and Pancreas in The Royal College of Surgeons of Edinburgh from 17 to 23 October 1993. The course is intended for discussion of complex issues with an audience composed of relatively senior specialist surgeons. Topics to be covered will include: cholelithiasis and choledocholithiasis; minimally invasive hepatobiliary surgery; transplantation of liver and pancreas; acute and chronic pancreatitis; pancreatic and periampullary cancer; hepatobiliary trauma; portal hypertension; and hepatic and biliary malignancy. The course will be directed by Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh.

Further information can be obtained from: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK.

D. C. Carter

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799–801

Pharmacological study of the internal anal sphincter in patients with chronic anal fissure

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A pharmacological study of the internal anal sphincter (IAS) was undertaken in patients with chronic anal fissure. The sensitivity of the IAS to the contractile effect of phenylephrine and potassium chloride and to relaxation by isoproterenol was evaluated. Supersensitivity of the IAS to relaxation by isoproterenol was noted. Further research is necessary to determine the pharmacological basis of such a disturbance.

Chronic anal fissure is defined as an ulcer of the anal canal distal to the pectinate line. In 76 per cent of patients the lesion is in the posterior anal verge[1–4]. The internal anal sphincter (IAS) is located at the level of the anal canal and formed by the thickening of the smooth circular muscle layer of the rectum. Autonomic nerves supply the IAS: parasympathetic innervation is from the pelvic nerves and the sympathetic supply from the hypogastric nerves. The sympathetic excitatory effect is noradrenergic and antagonized by α-blockers[5–8]. Patients with anal fissure have increased anal resting pressure, as measured by electromanometrical methods[3,4,9–17]. Such a functional disturbance of the IAS may be involved in the aetiology of anal fissure.

The aim of this research was to study samples of IAS obtained from patients with chronic anal fissure to determine the *in vitro* pharmacological reactivity of such smooth muscle. The contractile effects induced by phenylephrine were studied as were those of a selective α-adrenergic receptor agonist and the relaxation induced by isoproterenol, a selective β-adrenergic receptor agonist. The contractile effects of potassium chloride were also studied because this compound induces pharmacological receptor-independent contractions.

Patients and methods

Samples from a total of 12 patients were used. The control group comprised five patients with third-degree haemorrhoids and a normal anal canal resting pressure who were treated surgically. The experimental group consisted of seven patients with chronic anal fissure and increased anal canal pressure who underwent lateral sphincterotomy.

All patients underwent spinal (peridural) anaesthesia and operation in the lithotomy position. A slice of the IAS parallel to the fibres and approximately 1·0 cm long, 0·5 cm wide and 0·2 cm thick was taken. In controls, removal of the muscle sample was carried out at the site of routine partial sphincterotomy without damage to the functional activity of the IAS. After excision, samples were immediately immersed in Krebs–Henseleit solution of composition: NaCl, 115·0 nmol/l; KCl, 4·7 nmol/l; $CaCl_2$, 2·5 nmol/l; KH_2PO_4, 1·2 nmol/l; $MgSO_4$, 2·5 nmol/l; $NaHCO_3$, 24·0 nmol/l; and 11·0 nmol/l glucose containing 20 mg/l ascorbic acid to prevent oxidation of the catecholamines. The muscle segments were held by the extremities in the direction of the fibres and suspended in a 35-ml organ bath containing Krebs–Henseleit solution at 36·5 ± 0·1°C and gassed with 95 per cent oxygen–5 per cent carbon dioxide. Segments were attached to an isometric transducer coupled to a polygraph recorder (DMP4; Narco Bio-Systems, Houston, Texas, USA). An initial tension of 2·0 g was applied. Ionic equilibration was allowed to occur over the following 1 h and the electrolyte solution was exchanged every 15 min.

Dose–response curves

After a period of equilibration, a cumulative concentration–response curve was obtained for each of phenylephrine, potassium chloride and isoproterenol. The maximum effect of each agonist was determined when three consecutive increasing concentrations increased the response by < 10 per cent compared with the previous concentration. The sensitivity of the IAS was measured using EC_{50} values (concentration producing half-maximal response). EC_{50} values were expressed as geometric mean (95 per cent confidence interval)[18] and sensitivity estimated by the concentration ratio of the EC_{50} values (EC_{50} control/EC_{50} experimental).

Drugs

Solutions were prepared in double-distilled water that had been passed through a cation-exchange column. The drugs used were isoproterenol sulphate and phenylephrine hydrochloride (Sigma Chemicals, St Louis, Missouri, USA).

Statistical analysis

Results were compared using Fisher–Snedecor analysis of variance and Student's t test; $P \leqslant 0{\cdot}05$ was considered significant[19].

Results

Contractile effect of phenylephrine

Figure 1 shows that the dose–response curves were not different in the two groups studied. The mean EC_{50} of controls

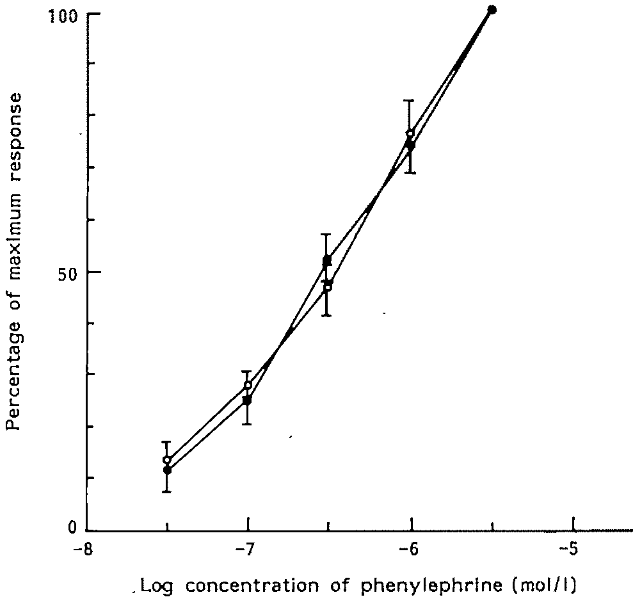

Figure 1 *Dose–response curves for phenylephrine in the isolated internal anal sphincter of control* (○) *and experimental* (●) *groups. Values are mean(s.e.m.)* (n = 5)

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Table 1 *Effect of phenylephrine on isolated internal anal sphincter*

	No.	EC_{50} (mol/l × 10^{-7})*	Concentration ratio†	Mean(s.e.m.) maximum response (g relaxation per 100 mg wet weight)
Control	5	3·32 (2·63–4·17)	—	1·18(0·18)
Experimental	5	2·91 (1·34–6·16)	1·14	1·19(0·45)

*Values are geometric mean (95% confidence interval); †EC_{50} control/EC_{50} experimental

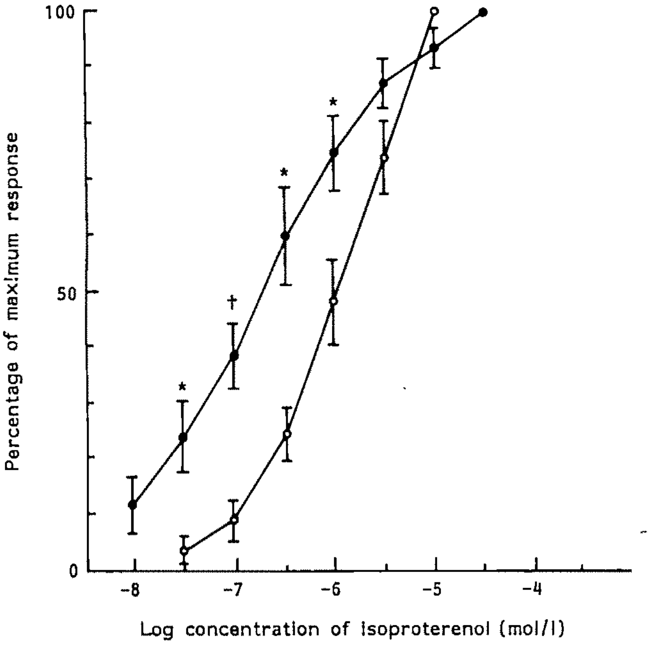

Figure 2 *Dose–response curves for isoproterenol in the isolated internal anal sphincter of control* (o) *and experimental* (●) *groups. Values are mean(s.e.m.)* (n = *4*). *P < *0·05;* †P < *0·01* (*Student's* t *test*)

Table 2 *Effect of isoproterenol on isolated internal anal sphincter*

	No.	EC_{50} (mol/l × 10^{-8})*	Concentration ratio†	Mean(s.e.m.) maximum response (g relaxation per 100 mg wet weight)
Control	4	1·75 (0·63–4·79)	—	0·83(0·13)
Experimental	4	0·15 (0·11–0·21)‡	11·67	0·88(0·42)

*Values are geometric mean (95% confidence interval); †EC_{50} control/EC_{50} experimental. ‡$P < 0·01$ (Student's *t* test)

(3·32 × 10^{-7} mol/l) did not differ significantly from that of the experimental group (2·91 × 10^{-7} mol/l); the concentration ratio was 1·14 (*Table 1*). There was no marked difference between the maximum responses induced by the drug in each group.

Relaxation effect of isoproterenol

Figure 2 shows that the dose–response curve obtained for isoproterenol was shifted to the left, indicating the presence of supersensitivity to the relaxation effect of this agonist. The mean EC_{50} of the experimental group (0·15 × 10^{-8} mol/l) was significantly different ($P < 0·01$) from that of controls (1·75 × 10^{-8} mol/l) (*Table 2*). The concentration ratio was 11·67. The maximum responses of each group were not significantly different.

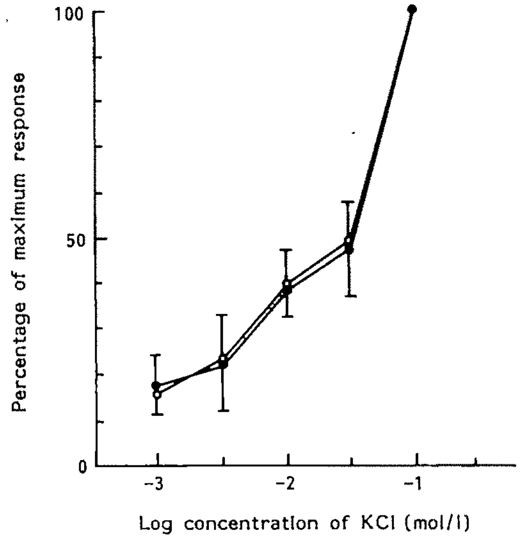

Figure 3 *Dose–response curves for potassium chloride in the isolated internal anal sphincter of control* (o; n = *5*) *and experimental* (●; n = *7*) *groups. Values are mean(s.e.m.)*

Table 3 *Effect of potassium chloride on isolated internal anal sphincter*

	No.	EC_{50} (mol/l × 10^{-2})*	Concentration ratio†	Mean(s.e.m.) maximum response (g relaxation per 100 mg wet weight)
Control	5	3·97 (2·51–6·02)	—	1·65(0·22)
Experimental	7	4·20 (3·38–5·01)	0·95	1·37(0·38)

*Values are geometric mean (95% confidence interval); †EC_{50} control/EC_{50} experimental

Contractile effect of potassium chloride

Figure 3 shows that the curve for potassium chloride was the same in each group. There was again no significant difference between the maximum responses of the control and experimental groups (*Table 3*).

Discussion

This study demonstrates a similar sensitivity to phenylephrine and potassium chloride in tissues from control subjects and from those with anal fissure. The contractile response to potassium chloride was greater than that to phenylephrine. These findings suggest that the musculature of the IAS in patients with anal fissure is not changed.

A significant difference in sensitivity was found in the experimental group undergoing relaxation using isoproterenol. The dose–response curve was shifted to the left, characterizing a supersensitivity to β_2-agonists[18]. This supersensitivity might be induced by some pharmacological alteration, such as prolonged absence of the neurotransmitter, or by modifications at neurotransmitter or metabolic level. The molecular alteration might be at cellular receptor level, for example an increased number of receptors or a change in their structure[20]. The data do not allow comment on a possible link between IAS supersensitivity to isoproterenol and the alternative (and still unknown) non-cholinergic non-adrenergic inhibitory system[21].

Stress must be evaluated as a factor in the aetiology of anal fissure. Rats submitted to stress develop molecular changes in β_1-adrenergic receptors and these changes are linked with cortical and/or medullary adrenal hormones[20,22]. IAS supersensitivity to relaxation by isoproterenol in patients with chronic anal fissure could be the result of a modification of β-adrenergic receptors linked with altered cortical and/or medullary adrenal hormones[20,22]. Further research should be carried out to determine the molecular alteration responsible for IAS supersensitivity to isoproterenol.

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Total sphincter conservation in high fistula *in ano*: results of a new approach

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Mr R. K. S. Phillips

An intersphincteric approach has been developed that allows complet sphincter preservation in some patients with high fistulas. This operatio in 13 patients (eight trans-sphincteric, five suprasphincteric tracks) ha resulted in complete success in seven, partial success (ultimate sacrific of the internal anal sphincter) in two and failure in four. When th operation is successful continence is better than after failed procedures.

High trans-sphincteric, suprasphincteric and rectovaginal fistulas are a particular surgical challenge, especially when they occur in patients with inflammatory bowel disease. Any form of sphincter division may lead to a deficit in continence, which can be made more pronounced by concurrent bowel resection or diarrhoea. Preservation of both external and internal anal sphincters can be achieved by anal mucosal or full-thickness advancement flaps but, because of disappointing personal results with these techniques, an alternative method has been developed and employed in a group of patients with these challenging fistulas, some of whom have also had inflammatory bowel disease.

Patients and methods

Patients

Between June 1989 and October 1991 the following procedure was performed in 13 patients, all of whom had previously undergone unsuccessful operations. There were seven men and six women with a mean age of 42 (range 16–66) years, five of whom had inflammatory bowel disease. Rectovaginal fistulas were present in three patients; the tracks were high trans-sphincteric in eight and suprasphincteric in five.

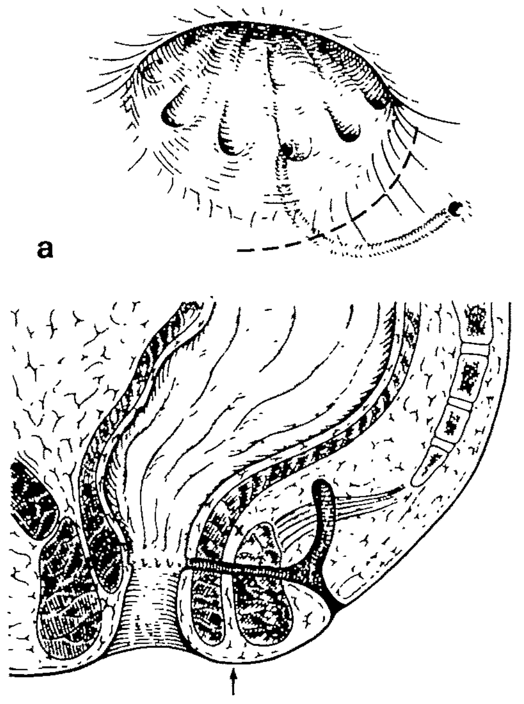

Figure 1 *Operating procedure:* **a** *a curvilinear incision is made over the intersphincteric groove between the external opening and the anus;* **b** *the incision is deepened in the intersphincteric space (arrow) and continued for 1–2 cm beyond the primary track (x marks the cephalad extent of the dissection)*

Surgical technique

The essential steps of the operation are: (1) eradication cryptoglandular sepsis from the intersphincteric space by a intersphincteric approach; (2) closure of the internal opening fro within the intersphincteric space; (3) total excision of the fistul complex; (4) primary repair of the track across the external sphincte and (5) primary wound closure under antibiotic cover.

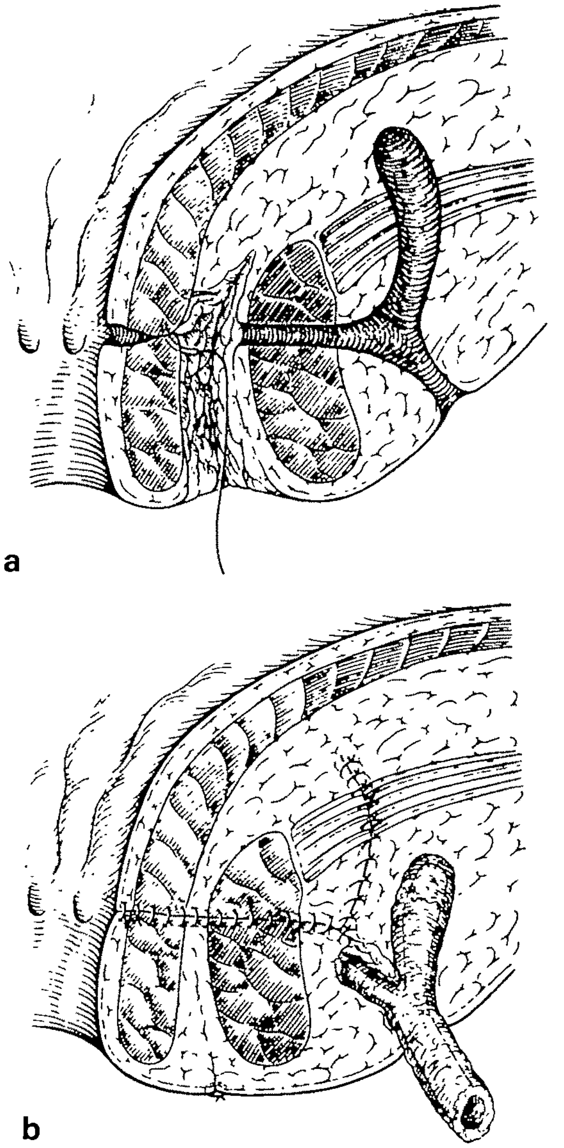

Figure 2 **a** *The opening in the internal sphincter is oversewn with 2/ polyglactin from within the intersphincteric space;* **b** *the track outsid the external sphincter is excised and the defects in the striated muscle repaired before primary wound closure*

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As many of the fistulas were complex in their geography (that is, the track to the anus was not straight or there were secondary extensions), it was helpful to divide each fistula into the component outside the external sphincter and the presumed aetiological component in the intersphincteric space. This was achieved with a curvilinear incision between the external opening and the anus overlying the intersphincteric groove; this incision was deepened within the intersphincteric space to reach the fistula as it travelled between the external and internal anal sphincters (*Figure 1*). The approach is similar to that adopted during dissection for either postanal repair or intersphincteric excision of the rectum. The inflammation can lead to some bleeding unless steps are taken to counter this. One method is infiltration with a dilute solution of adrenaline, but in the present patients the entire dissection was performed using the diathermy spatula and a high coagulating current, which results in a completely dry field. Once the track had been divided it was found helpful to continue the dissection for a further 1–2 cm cephalad as this facilitated closure of the internal opening, which was performed from the intersphincteric space using an absorbable material (2/0 polyglactin) (*Figure 2*). The primary track was then completely excised with any secondary extensions and the resultant hole in the external sphincter repaired with the same suture material. Finally, the wound was closed primarily. Perioperative gentamicin and metronidazole were used in all patients.

Success was evaluated in terms of preservation of sphincter function. Slight wound dehiscence or a submucosal infection, which on two occasions needed surgical attention, did not prevent ultimate success. Furthermore, partial success with preservation of the external sphincter but ultimate sacrifice of the internal sphincter (two patients) was also possible.

Results

The mean follow-up in the 13 patients is 22 (range 4–33) months. Complete success with preservation of both external and internal anal sphincters was achieved in seven patients and in a further two there was partial success (*Table 1*). Thus the external sphincter was preserved in nine of the 13 patients. Where the sphincters had been completely preserved, six patients were normally continent after surgery; the seventh, a woman with Crohn's disease, is occasionally incontinent to flatus.

The technique failed in four patients; one was a 28-year-old woman who had ulcerative colitis and an ileorectal anastomotic stricture. She has subsequently undergone fistulotomy under the protection of a loop ileostomy and awaits sphincter repair before anastomotic dilatation and ileostomy closure. Two further patients are incontinent to flatus and the last has occasional episodes of incontinence to liquid.

Discussion

The aetiology and pathogenesis of non-specific fistula *in ano* remain under discussion[1]. The central issue in the cryptoglandular hypothesis is infection in the intersphincteric space[2], and traditional treatment has accordingly involved division or excision of that segment of internal anal sphincter below the track. Parks *et al.*[3] acknowledged that, although division of the internal sphincter caused little loss of function in most cases, in elderly women with weak sphincters it may cause partial incontinence. Bennett and Goligher[4] assessed the functional outcome in patients who underwent internal sphincterotomy for treatment of anal fissure and found rates of partial incontinence to flatus and faeces at 3 years after surgery to be 13 and 9 per cent respectively. In addition, there was a 28 per cent incidence of soiling, a symptom that did not improve with time. In the normal population these authors found a 10 per cent incidence of flatus incontinence, a 3 per cent incidence of incontinence to faeces and a 2 per cent incidence of soiling[4]. The development of techniques for assessing anorectal physiology led to the association of internal sphincter division with a fall in the resting pressure in the distal anal canal[5–7]. Interestingly, Bennett and Goligher[4] found no clear correlation between the occurrence of functional defects and the amount of internal sphincter divided. Impairment of continence may have a further aetiological component in changes in mucosal sensation[8], a factor that might well arise from scarring and deformity after fistula surgery.

The case for preservation of the external sphincter has always been much stronger: not only are the potential consequences of sacrifice of the striated muscle more disastrous but, if the cryptoglandular hypothesis is correct, then adequate treatment of the intersphincteric pathology should lead to healing

Table 1 *Summary of the results of 13 patients with fistula* in ano *treated by excision and primary closure*

Patient no	Sex	Age (years)	Disease	Fistula	Initial result	Further surgery	Sphincter preservation: Internal	Sphincter preservation: External	Continence grade*
1	F	55	Ulcerative colitis	Anterior suprasphincteric rectovaginal	Submucous fistula	Fistula laid open	Yes	Yes	1
2	F	38		Anterior trans-sphincteric	Primary healing	None	Yes	Yes	1
3	F	36	Crohn's	Anterior trans-sphincteric supralevator extension	Submucous fistula	Fistula laid open	Yes	Yes	2
4	M	39		Anterior trans-sphincteric	Primary healing	None	Yes	Yes	1
5	F	16		Anterior suprasphincteric rectovaginal	Primary healing	None	Yes	Yes	1
6	F	32		Anterior trans-sphincteric	Primary healing	None	Yes	Yes	1
7	M	57		Anterior trans-sphincteric	Primary healing	None	Yes	Yes	1
8	M	51		Anterior trans-sphincteric	Intersphincteric fistula	Fistula laid open	No	Yes	1
9	M	39		Anterior trans-sphincteric	Intersphincteric fistula	Fistula laid open	No	Yes	1
10	M	57	Crohn's	Posterior suprasphincteric	Trans-sphincteric fistula	Loose seton (1), tight seton (2), track laid open	No	No	2
11	M	66		Posterior suprasphincteric	Trans-sphincteric fistula	Loose seton (1), tight seton (1), track laid open	No	No	2
12	M	36	Crohn's	Anterior trans-sphincteric, intersphincteric abscess	Trans-sphincteric fistula	Loose seton (1), tight seton (1), track laid open	No	No	3
13	F	28	Ulcerative colitis	Anterior suprasphincteric rectovaginal, perineal abscess	Trans-sphincteric fistula	Loop ileostomy, fistula laid open	No	No	4

*Grades: 1, fully continent; 2, incontinent to flatus; 3, incontinent to liquid; 4, totally faecally incontinent or stoma irrespective of any specific treatment to the track outside the intersphincteric space.

Several techniques have been advocated with the aim of external sphincter preservation. These include the use of various forms of seton (chemical[9,10], loose[11], tight[12]), excision and primary repair of divided structures[13], endoanal advancement flaps[14–20] and rerouting of the track[21]. Chemical setons include those ayurvedic treatments practised in India that involve the weekly insertion into the fistula of a specially prepared thread coated with herbs, the alkalinity of which renders the thread caustic. Thomson and Ross[11] found the loose seton method to be successful in preserving the external sphincter without recourse to its division to allow fistula healing in 44 per cent of patients; higher success rates have been reported with the same technique in the management of anterior as opposed to posterior fistulas[22]. The reported success of endoanal flaps has not been reflected in the present authors' experience; the theoretical advantage of the method described is that it avoids flap mobilization and the potential hazards of ischaemic necrosis and anastomotic breakdown associated with that manoeuvre.

As long as sepsis is eliminated from the intersphincteric space, closure of the curetted track running through the internal sphincter under antibiotic cover should suffice, and in this respect should be more successful than simple closure from the mucosal aspect. The failures in the present series all occurred less than 30 days after surgery and probably relate to continuing sepsis. Closure of the holes in the sphincters combined with coring out of the extrasphincteric component of the track with primary wound closure is much simpler in practice than excision by division followed by reconstitution, this latter technique requiring meticulous attention to repair of divided muscles[13]. Primary wound closure, if successful, offers the advantages of reduced healing time and less residual scarring and deformity. The method described does not compromise conventional treatment in the failures, since the sphincter anatomy is totally preserved.

The technique described appears to be less successful in patients with fistula in association with inflammatory bowel disease. Results of the advancement flap technique suggest that patient selection in this group may be important and that active rectal involvement is a contraindication to that method[16,20]. The construction of a diversionary stoma in such cases might improve the success rate, although this has not necessarily been the case with advancement flaps[16].

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Figures 1 and *2* were drawn by Gillian Lee.

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SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, June, 805–806

A selection from the May issue of the American journal.

Intestinal fatty acid binding protein in serum and urine reflects early ischemic injury to the small bowel

Gerald Gollin, MD, Christine Marks, BA, *and* **William H. Marks, MD, PhD,** *New Haven, Conn.*

Background. *Intestinal fatty acid binding protein (I-FABP) is a 15 kd protein that constitutes 2% to 3% of enterocyte protein. Normally I-FABP is undetectable in serum. The purpose of this study was to determine whether I-FABP could be detected in peripheral serum and/or urine early in the evolution of intestinal ischemic injury.*
Methods. *I-FABP and two putative biochemical markers of mesenteric ischemia, hexosaminidase and lactate dehydrogenase, were quantitated in the serum of rats subjected to mesenteric ischemia produced by (1) 0.5 hours, 1 hour, or 3 hours of superior mesenteric artery (SMA) occlusion followed by reperfusion; (2) 1 hour of mesenteric occlusion to a 10 cm segment of jejunum followed by reperfusion; and (3) arterial ligation to a 10 cm segment of jejunum without reperfusion. I-FABP was also quantitated in the urine and intestinal mucosa of these animals.*
Results. *The baseline serum I-FABP level was* ≤ 4.0 *ng/ml in all animals. In control animals, I-FABP remained unchanged throughout the experiment. In the ischemia/reperfusion groups, I-FABP immediately appeared in the serum on reperfusion. With segmental arterial ligation, I-FABP was detected in the serum within 15 minutes. Urinary content of I-FABP rose 60 minutes after its initial appearance in the serum, and its elimination paralleled serum I-FABP levels. Serum hexosaminidase and lactate dehydrogenase levels only rose after 3 hours of SMA occlusion with reperfusion. One hour of SMA occlusion and reperfusion resulted in only mild to moderate mucosal injury, whereas 3 hours of SMA ischemia with reperfusion produced areas of transmural necrosis.*
Conclusions. *I-FABP is released into the peripheral circulation after reversible intestinal ischemic injury and has potential as a biochemical marker to facilitate the early detection of mesenteric ischemia. (SURGERY 1993;113:545–51.)*

Comparative cardiopulmonary effects of carbon dioxide versus helium pneumoperitoneum

Thomas A. Leighton, MD, Se-Yuan Liu, MD, *and* **Frederic S. Bongard, MD,** *Torrance, Calif.*

The recent surge in enthusiasm for laparoscopic surgery has created concern that abdominal insufflation with carbon dioxide produces a respiratory acidosis. This may be because of both transperitoneal gas absorption and impaired ventilation with increased dead space from elevated intraabdominal pressure. To examine the relative contributions of these factors, we developed an animal model of surgical pneumoperitoneum that evaluated the cardiorespiratory effects of abdominal insufflation. Helium was chosen as an alternative to CO_2 *because it is both chemically and biologically inert. Carbon dioxide absorption during* CO_2 *pneumoperitoneum caused arterial* P_{CO_2} *to increase from* 41.3 ± 3.0 *to a maximum of* 58.3 ± 4.0 *mm Hg, with pH descending from* 7.46 ± 0.02 *to a nadir of* 7.31 ± 0.02 $(p < 0.05)$*. Pulmonary artery pressure increased to twice baseline levels during* CO_2 *insufflation* $(p < 0.05)$*. Helium did not cause hypercarbia, acidemia, or pulmonary hypertension despite insufflation under identical conditions. These results indicate that transperitoneal absorption of* CO_2*, not increased dead space, is responsible for the respiratory acidosis observed. Helium merits further study as an agent to induce pneumoperitoneum, especially when concerns of underlying acidosis or impaired gas exchange are present. (SURGERY 1993;113:527–31.)*

Gastric intramucosal acidosis in patients with chronic kidney failure

Lawrence Diebel, MD, Robert Kozol, MD, Robert F. Wilson, MD, Sudesh Mahajan, MD, Daoud Abu-Hamdan, MD, *and* **Donald Thomas, MD,** *Allen Park and Detroit, Mich.*

Background. *Patients with chronic kidney failure have an increased incidence of gastrointestinal complications, particularly bleeding from the stomach. Diminished mucosal blood flow is thought to be an important etiologic factor for such bleeding.*
Methods. *Eleven patients with kidney failure on maintenance dialysis underwent placement of a gastric tonometer for the determination of gastric intramucosal pH* (pH_i) *before and during dialysis. The arterial pH* (pH_a)*, calculated* pH_i*, and* $pH_a - pH_i$ *differences were compared with the results in a control group of seven normal volunteers.*
Results. *The patients with chronic kidney failure had a mean (±SD)* pH_a (7.36 ± 0.04) *similar to that found in seven control subjects* (7.37 ± 0.04)*. However, the gastric mucosal pH in the patients on dialysis* (7.20 ± 0.17) *was lower than in the seven control subjects* (7.38 ± 0.06) $(p < 0.01)$*. A gastric mucosal pH thought to be predictive of either bleeding from stress ulceration* $(pH_i < 7.32)$ *or mucosal ischemia* $(pH_i - pH_a$ *difference* $>0.13)$ *was found in nine (82%) of the patients with kidney failure and in only one (14%) of the control subjects* $(p < 0.001)$*.*
Conclusions. *This new preliminary finding suggests that the high incidence of gastric bleeding in chronic kidney failure may be related to mucosal ischemia. (SURGERY 1993; 113:520–6.)*

Submucosal tumors of the stomach: A study of 100 operative cases

Takafumi Bandoh, MD, Touru Isoyama, MD, *and* **Hiroshi Toyoshima, MD,** *Tokyo, Japan*

Background. *Mass screening for gastric cancer has been established in Japan, and asymptomatic submucosal tumors are often detected. This retrospective study was made to evaluate the proper surgical management of malignant submucosal tumors of the stomach.*
Methods. *One hundred submucosal tumors of the stomach were surgically resected, irrespective of symptoms and size. Up to 45% of these tumors, including 44 myogenic lesions, 23 non-Hodgkin's lymphomas, and 11 schwannomas, proved malignant. Myogenic sarcomas were classified in low and high grades according to mitotic rates, cellularity, and pleomorphism.*
Results. *Thirty-five of 55 benign tumors and four of nine low-grade sarcomas underwent enucleation only, without recurrence. The remaining five low-grade and 11 high-grade sarcomas were treated by radical gastrectomy; the 5-year survival was 100% for the former and 80% for the latter. Eighteen patients with lymphomas underwent total or subtotal gastrectomy, and three patients underwent noncurative resection; the 5-year survival rates were 54.2% and 0%, respectively, with a clear significant difference ($p < 0.001$). Adjuvant chemotherapy was significantly superior to surgery alone ($p < 0.05$). Other factors did not affect survival of lymphoma.*
Conclusions. *With these observations, we believe that following the patients with submucosal tumor without surgery is not reasonable. Enucleation will suffice for low-grade sarcomas and benign tumors; high-grade sarcomas can be well treated by gastrectomy. Total or subtotal gastrectomy with systematic lymph node dissection when performed for cure can provide good results for resectable lymphomas.* (SURGERY *1993;113:498–506.)*

Patterns of lung involvement by malignant lymphoma

Steven J. Mentzer, MD, John J. Reilly, MD, Arthur T. Skarin, MD, *and* **David J. Sugarbaker, MD,** *Boston, Mass.*

Background. *Recent evidence has suggested that the anatomic distribution of malignant lymphomas may reflect important differences in biologic behavior. To determine if the anatomic distribution of malignant lymphomas in the lung correlated with the disease course, we examined the pattern of lung involvement in patients with Hodgkin's and non-Hodgkin's lymphomas.*
Methods. *We reviewed the medical records of 651 patients with a diagnosis of malignant lymphoma and identified 54 patients with histologically documented lung involvement. Based on radiologic and surgical findings, these patients had lung involvement characterized as either (1) bronchovascular–lymphangitic, (2) nodular, or (3) alveolar. The pattern of lung involvement was correlated with clinical manifestations and disease course.*
Results. *Distinct clinical courses were associated with these three patterns of lung involvement. In contrast, traditional histopathologic classification did not correlate with the pattern of lung involvement or the disease course in these 54 patients. An alveolar pattern of lung involvement was a poor prognostic factor and was associated with a median survival of $12\frac{1}{2}$ months. Pleural effusions eventually developed in 24 patients and were associated with a median survival of only 3 months.*
Conclusions. *These findings suggest that the anatomic pattern of lung involvement is a measure of biologic behavior and may be a useful variable in the staging of patients with malignant lymphoma.* (SURGERY *1993;113:507–14.)*

Regulation of small intestinal glutamine transport by epidermal growth factor

Rabih M. Salloum, MD, Bruce R. Stevens, PhD, Gregory S. Schultz, PhD, *and* **Wiley W. Souba, MD, ScD,** *Gainesville, Fla.*

Background. *Epidermal growth factor (EGF) stimulates cell replication and increases DNA content of the small intestine, but its effects on mucosal amino acid transport are unknown.*
Methods. *To investigate these effects, we treated adult rats with vehicle or EGF (10 μg/100 gm body weight subcutaneously every 8 hours for three doses). Jejunal brush border membrane vesicles (BBMVs) from each group were prepared by Mg^{++} aggregation/differential centrifugation. BBMVs were enriched fifteenfold in alkaline phosphatase, indicating BBMV purity. Transport of ^3H-glutamine and ^3H-alanine was studied by a rapid mixing filtration technique. Uptakes were primarily Na^+ dependent, occurred in an osmotically active space, exhibited classic overshoots, and had similar 2-hour equilibrium values.*
Results. *Glutamine transport by BBMVs more than doubled in rats treated with EGF (16.4 ± 0.1 pmol glutamine/mg protein/10 sec in EGF vs 7.1 ± 0.5 pmol glutamine/mg protein/10 sec in controls; $p < 0.001$). Kinetic studies of the glutamine transporter showed that the increase in transport was the result of a 70% increase in maximal transport velocity (total maximum glutamine uptake = 193 ± 8 pmol glutamine/mg protein/10 sec in EGF vs 114 ± 7 pmol glutamine/mg protein/10 sec in controls; $p < 0.0001$) with no change in transporter affinity (transporter affinity = 224 ± 6 μmol/L in EGF vs 242 ± 37 μmol/L in controls; difference, not significant). Alanine uptake by BBMVs was also increased with EGF administration (10.2 ± 2.0 pmol alanine/mg protein/10 sec in EGF vs 4.5 ± 0.5 pmol alanine/mg protein/10 sec in controls; $p < 0.005$). Simultaneously, glucose transport was decreased by 50% in EGF-treated rats, indicating that the Na^+-dependent glucose cotransporter is regulated independently from and opposite to amino acid transporters.*
Conclusions. *We conclude that EGF up-regulates amino acid transport activity in jejunal BBMVs, an event that is most likely caused by an increase in de novo biosynthesis of transporter protein. The increase in amino acid uptake not only may support de novo protein synthesis but, in the case of glutamine, also may be required for energy production and nucleotide biosynthesis.* (SURGERY *1993;113:552–9.)*

Correspondence

Prospective randomized trial comparing the Shouldice technique and plication darn for inguinal hernia

Sir

I was disappointed with the recent article (*Br J Surg* 1992; 79: 1068–70) by Messrs Kingsnorth, Gray and Nott. The data presented do not support the authors' conclusions that (1) repair failed more often in residents' than in consultants' hands and (2) the higher rate of failure was experience based. The consultant's 4 per cent recurrence rate (one of 25) for Shouldice repair is lower than the 4·8 per cent rate (six of 126) for similar repair performed by the residents. While this may be statistically significant, it is clearly not clinically relevant and does not logically lead to the conclusion that 'the high failure rate of the operation was attributable to the inexperience with this technique in the junior surgeons'. There is no evidence that the higher failure rate in the Shouldice repair was due to average resident failure or ability to perform hernia surgery competently. Indeed, one resident had two recurrences of Shouldice repairs. If this surgeon had the average number of nine Shouldice repairs per resident, the remaining residents' recurrence rate would have been four of 117 (3·4 per cent). To condemn the residents' proficiency is not only unfair but unjustified by the data presented. If the consultant had had one more recurrence, the results would have been clearly in favour of the residents on all counts. Furthermore, if one compares the residents' experience with the plication darn repair (2·7 per cent recurrence rate) with the consultant's Shouldice experience (4 per cent recurrence rate), one might logically argue that the plication darn repair is superior to the Shouldice operation or that the residents were better surgeons. To use statistics with small numbers can distort clinical relevance.

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Authors' reply

Sir

Thank you for giving us the opportunity to reply to the letter from Dr Aust, whose disappointment arises from the fact that he has failed to appreciate that the *P* value in the abstract was accompanied by a 'greater than' rather than a 'less than' symbol, i.e. none of the comparisons between groups of patients was statistically significant. The observations (not conclusions, as there is no statistical significance) we have drawn from our results are therefore speculative. We have been careful to make statements such as 'the trial has *not* shown superiority of Shouldice repair over plication darn' and 'the recurrences *suggest* that additional supervision of junior surgeons is required during the Shouldice repair learning period'.

Our results with plication darn were similar to those achieved in centres worldwide whereas our findings with the Shouldice repair fell well below all reports published before the end of our study. Because collectively 83 per cent (126 of 151) of the Shouldice repairs were carried out by juniors, we hold to our opinion that more intensive training (see paragraph two in the Discussion of our paper) is required to achieve a Shouldice Clinic recurrence rate under 1 per cent.

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Statistical comment

Essentially, I agree with Dr Aust. Mr Kingsnorth and colleagues report a randomized trial comparing two methods of inguinal hernia repair that fails to detect a striking difference between the two approaches. The sample size was rather modest, with the main comparison being based on seven recurrences *versus* four, so that the negative finding is weak. Where I take issue with Mr Kingsnorth and co-workers is that, instead of simply reporting this finding based on the randomized comparison, they embark on a non-randomized comparison of the one consultant with 14 junior surgeons. Even if this comparison did show a difference, it might simply reflect some systematic bias in how cases were allocated to surgeons. However, as Dr Aust points out, when one makes this comparison with due allowance for the number of procedures undertaken, one ends up by comparing one in 25 (4 per cent) with six in 125 (4·8 per cent). This difference is clearly of neither statistical nor clinical significance and is in any case based on an unsound comparison.

G. D. Murray

Statistical Consultant

Endoscopic sphincterotomy, nasobiliary drainage and biliary stent placement without image intensification

Sir

Drs Misra, Agarwal and Gupta from India report (*Br J Surg* 1992; 79: 1179–80) 175 endoscopic retrograde cholangiopancreatography (ERCP) procedures without the aid of an image intensifier. This is certainly unusual and the results are astonishing. The statement that 'ERCP was successful in 168 patients (96 per cent)' is remarkable, but the claim that 'no procedure-related complications were seen' is even more striking. Complete lack of complications in a series of this size (including many therapeutic procedures) has never been reported before and flies in the face of all anecdotal and published evidence. The complication rate in my unit during the last 2000 procedures averaged 6·4 per cent. Do the authors attribute their remarkable results to the unconventional technique or is there another explanation?

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Authors' reply

Sir

Thank you for allowing us to answer the letter from Dr Cotton. We originally sent a full paper for consideration for publication in the Journal, but it was accepted only as a Short Note and certain details were omitted in the shortening. The absence of cholangitis in the series is probably because patients with biliary obstruction were subjected to endoscopic retrograde cholangiopancreatography (ERCP) on the day they were to undergo operation; otherwise a stent or nasobiliary drain was placed in the common bile duct. Complications of sphincterotomy depend largely on the length of the cut. We err on the side of caution and make a relatively small sphincterotomy. The complication rate of 6·4 per cent reported by Dr Cotton may perhaps be related to less fit patients being treated at his centre.

Endoscopists are not used to performing ERCP and related procedures without an image intensifier because they have never been without one. At our centre we work in difficult circumstances where even basic amenities are sometimes lacking. We do not recommend the lack of an image intensifier but are obliged to attempt these procedures in adverse conditions. Of late, we do not have facilities for radiology, but still perform sphincterotomy, nasobiliary drainage and stent placement in the endoscopy room.

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The resubmitted Short Note contained the words: 'No procedure-related complications were seen'. The original full-length paper described one patient who developed a pancreatic abscess following ERCP and another two with 'transient abdominal pain'.

Editor

Controlled trial of wound infiltration with bupivacaine for postoperative pain relief after appendicectomy in children

Sir

I read with interest the article by Dr Wright (*Br J Surg* 1993; **80**: 110–11) on wound infiltration for relief of postoperative pain. Whereas it has been documented that infiltration of bupivacaine locally does lessen postoperative pain, the exact time at which it should be given during the operation is important. It is unclear from the data presented whether there was any statistical difference in the perception of pain in the two groups of patients either 1 or 8 h after operation. Bupivacaine has a slow onset of action, taking as long as 30 min for its full effect and lasting 8 h. As an uncomplicated appendicectomy does not take long, it is appropriate to infiltrate bupivacaine before skin incision. This manoeuvre not only ensures the full analgesic effect of the drug at recovery but also allows haemostasis to be achieved from an inadvertently punctured vessel (which might otherwise have caused a wound haematoma).

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Rectal cancer risk in patients treated for familial adenomatous polyposis

Sir

We agree with Dr De Cosse and colleagues (*Br J Surg* 1992; **79**: 1372–5) that total colectomy with ileorectal anastomosis (IRA) is the preferred primary procedure for most patients with familial adenomatous polyposis (FAP). Our preference for IRA is based on the increased morbidity and mortality rates associated with restorative proctocolectomy (RPC)[1] and the current unacceptability of a permanent stoma with total panproctocolectomy. Many of these patients will eventually require proctectomy because of malignant change or increased cancer risk. De Cosse prefers IRA because the cumulative incidence of subsequent rectal cancer was *only* 13·1 per cent at 25 years. This incidence is increased to 14·2 per cent when three patients with rectal cancer diagnosed within 1 year of IRA were included. If the choice of surgical technique rests on subsequent cancer risk alone, then RPC or panproctocolectomy must surely be preferred, as these procedures remove all risk of subsequent colorectal carcinogenesis. The 'low' risk of rectal cancer of 14·2 per cent at 25 years is based on a sample of patients without massive rectal polyposis. These patients selected for IRA are at lower risk for subsequent rectal cancer compared with those who have been selected for total proctectomy. Patients with massive rectal involvement and who are at high risk of subsequent rectal carcinogenesis would have had their rectum removed with RPC or panproctocolectomy. If IRA is performed for these latter patients, a higher incidence of rectal cancer must undoubtedly follow. This high risk would steer the surgeon in the direction of total protectomy.

The 14·2 per cent incidence of rectal cancer at 25 years must therefore be regarded as the minimum expected incidence occurring in a selected group of patients with FAP with a lower risk of rectal cancer. Furthermore, the cumulative probability for subsequent proctectomy after IRA for multiple large polyps or severe dysplasia was 30·9 per cent at 25 years in their study. This must surely be regarded as surgery to prevent malignancy.

If IRA is more commonly performed and for the wrong reasons, a much higher incidence of subsequent rectal cancer will surely follow.

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1. Madden MV, Neale KF, Nicholls RJ *et al.* Comparison of morbidity and function after colectomy with ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis. *Br J Surg* 1991; **78**: 789–92.

Management of Gulf War casualties

Sir

I read with interest the article by Dr Souka (*Br J Surg* 1992; **79** 1307–8). I note that, in 84 casualties undergoing surgery, most of the wounded soldiers had soft tissue injuries and debridement was a majo treatment. It is true that debridement is a primary technique in treatment of any gunshot wounds. No detail was given, however, on debridement methods, in particular how to identify necrotic tissue. This is important to minimize the risk of infection and allow rapid wound healing.

I would like to recommend a special pair of spectacles designed to guide the extent of debridement required. The spectacles are made from glass transmitting light of a certain wavelength to help distinguish viable from non-viable tissue. Viable tissue appears pale and non-viable tissue dark, with a clear-cut transition that allows a more rational debridement. These spectacles were used for wound debridement in more than 300 injured patients, including some with gunshot wounds, and were especially helpful to inexperienced surgeons[1]. The clinical and pathological results show that the quality of debridement was improved.

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1. Xiaobing F, Huiming T, Chihyong S, Yinqui L. Special spectacles facilitating debridement: a report of their use in 300 cases. *Injury* 1992; **23**: 64–6.

Choice of agent for peripheral thrombolysis

Sir

I read with interest the article by Mr Earnshaw and colleagues (*Br J Surg* 1993; **80**: 25–7). There are two points on which I would like to comment. First, in the introduction the authors state that the cost of a 24-h treatment with tissue plasminogen activator (tPA) is ten times that with streptokinase. This statement is an oversimplification of cost and is merely comparing the prices of the two pharmaceuticals and not the procedure. Thrombolysis can be accelerated using various techniques to deliver high-dose tPA, and a short procedure time usually diminishes costs. At our institution the vast majority of thrombolytic procedures are completed in a working day, obviating the need for an overnight stay in the intensive care unit[1]. This saving in itself is greater than the price differential between the drugs.

Second, the traditional technique for low-dose infusion of the thrombolytic agent is being replaced by more aggressive ancillary catheter procedures, such as suction thrombectomy to debulk the thrombosed vessel or graft, thereby reducing the quantity of thrombolytic agent required and accelerating the procedure. It is our routine practice to treat infrainguinal thrombotic and embolic occlusions with this technique initially. Since adopting this protocol we have found a small but appreciable percentage of patients requires no thrombolytic agent at all.

The final paragraph in Mr Earnshaw's paper is important and an admirable summary of the relative insignificance of the actual choice of thrombolytic agent in the face of rapidly evolving mechanical devices and pharmaceutical delivery systems.

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1. Buckenham TM, George CD, Chester JF, Taylor RS, Dormandy JA. Accelerated thrombolysis using pulsed intra-thrombus recombinant human tissue type plasminogen activator (t-PA). *Eur J Vasc Surg* 1992; **6**: 237–40.

Clinical effects and therapy of endotoxaemia

Sir

The control of endotoxin has been of concern since Billroth in 1865 found that parenteral administration of ordinary distilled water to dogs was followed by a fever, and introduced the term pyrogen. More recently, the possible role of endotoxin has been examined in a variety of settings in current surgical and anaesthetic practice such as burns, obstructive jaundice, liver transplantation[1], cardiac surgery[2] and trauma.

The paper by Messrs Welbourn and Young[3] described the inflammatory response to endotoxin and examined potential approaches to reverse this process, citing many mechanisms based on observations made either *in vitro* or in response to single doses of endotoxin administered to animals. There are many factors that differ between these experimental observations and clinical experience, such as the large species differences in susceptibility to endotoxin (humans being the most sensitive species) and the lag phase between septic or traumatic insult and the onset of organ failure. For example, levels of endotoxin increase by up to 20 times after exposure to antibiotics, active or inactive against the cell wall, and yet there is no evidence to support (rather, some evidence to refute) the concern that the rapid destruction of bacteria with antibiotic therapy might 'aggravate' Gram-negative septicaemia[4].

The therapeutic approaches that Wellbourn and Young described warrant some comment. Although it is true that steroids are of no benefit in septic shock, the reason is likely to be more complex than that given, as steroids are of proven benefit in severe typhoid fever and meningitis. The encouraging findings of the cited antiendotoxin immunotherapy studies need to be balanced against those of four other series in which there was either no beneficial effect or an effect that was statistically marginal[5]. Moreover, for each monoclonal antibody cited, the benefit was limited to subgroups that were defined retrospectively, with no overall benefit to the study populations. In the polyclonal study, the immunoglobulin used appeared to reduce endotoxin levels and mortality rate and yet was characterized by a modest 4–8-fold rise in anticore glycolipid titre in comparison with the normal blood donor pool.

A convenient assay is urgently needed as the protective efficacy of various antiendotoxin immunotherapeutic agents in patients and in animal models correlates poorly with *in vitro* binding data[5]. The study by Reidy *et al.*[6] described such an assay using an animal model to study the efficacy of antiendotoxin antibodies *in vivo* by their effect on reversing endotoxin-induced changes in cardiac output. However, the derivation of the lipopolysaccharide that was studied and its resemblance to that found in patients is unclear. Moreover, the dose used to induce an effect in the rat (0·1 mg/kg) is 25 000 times higher on a weight basis than that required to induce similar changes in human volunteers (4 ng/kg)[7]. Although heat-killed vaccines for cholera and typhoid remain in current use, it would be more correct to say that the difficulty with human-derived vaccines is one of logistics rather than acceptance.

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1. Miyata T, Yokoyama I, Todo S, Tzakis A, Selby R, Starzl TE. Endotoxaemia, pulmonary complications and thrombocytopenia in liver transplantation. *Lancet* 1989; **ii**: 189–91.
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Regional variation in the surgical treatment of early breast cancer

Sir

We read with interest the recent article by Dr Morris (*Br J Surg* 1992; 79: 1312–13) on regional variation in the treatment of early breast cancer. During 1992 we sent a similar questionnaire to 985 consultant general surgeons in England and Wales; 589 replies were received, a response rate of 59·8 per cent. Some 134 surgeons returned the questionnaire indicating that they did no breast surgery, leaving 455 completed questionnaires. The response rate varied from 38 per cent (Mersey) to 75 per cent (London).

Surgeons were asked to state the preferred treatment of a premenopausal patient with a 2-cm tumour in the upper outer quadrant of the breast. In all, 354 (77·8 per cent) indicated that they would treat this conservatively by either tumorectomy or segmental mastectomy, 25 (5·5 per cent) that they would recommend mastectomy and 76 (16·7 per cent) that they would give the patient the choice of mastectomy or conservative surgery. Regional variations are shown in *Table 1*.

Table 1 *Results of postal questionnaire of consultants by region*

Region	No. of surgeons completing questionnaire	No. of surgeons recommending mastectomy
North	89	5 (6)
Central	100	8 (8·0)
South	220	5 (2·3)

Values in parentheses are percentages

Only 18 surgeons in England would recommend mastectomy as an initial treatment. There was a trend toward mastectomy being recommended more frequently in the central areas rather than in the north or south, but this difference was not statistically significant ($P = 0{\cdot}06$). We have been unable to duplicate the results of Dr Morris in our study with a larger response rate and would refute her suggestion that mastectomy is recommended by surgeons more frequently in the north.

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Simultaneous dynamic electromyographic proctography and cystometrography

Sir

I found the article by Mr Thorpe and colleagues (*Br J Surg* 1993; **80**: 115–20) fascinating and would strongly concur with the authors' conclusion that the pelvic floor must be studied as a whole. I am, however, somewhat surprised that they did not acknowledge the earlier work of Angus MacDonald, who reached similar conclusions indirectly from a simpler experimental model[1].

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1. MacDonald A, Shearer M, Paterson PJ, Finlay IG. Relationship between outlet obstruction constipation and obstructed urinary flow. *Br J Surg* 1991; **78**: 693–5.

Perioperative nutritional support

Sir

Some years have elapsed since we first questioned the dogma that the value of total parenteral nutrition for perioperative support was so logical as to make any clinical trial unethical[1]. I congratulate Messrs Moran and Jackson for their balanced Leading Article on this subject (*Br J Surg* 1993; **80**: 4–5). I agree that parenteral nutrition can be life-saving in patients with intestinal failure. The statement that it may be helpful in those who are severely malnourished needs to be qualified. When malnutrition is secondary to advanced malignant disease, there is no evidence that perioperative support is beneficial. Indeed, in our own study[2] it was clear that all patients with upper gastrointestinal malignancy whose serum albumin level at presentation was <30 g/l died within 1 year, had an operative mortality rate of 30 per cent and a major complication rate also 30 per cent.

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1. Woolfson AMJ, Smith JAR. Elective nutritional support after major surgery. *Clin Nutr* 1987; **8**: 15–21.
2. Burton S, Kay R, Simms JM, Smith JAR, Woods HF. Assessing the performance of prognostic nutritional indices. *Clin Nutr* 1983; **2**(Suppl): 0.92.

Contemporary management of the appendiceal mass

Letter 1

Sir

We read with interest the recent Review by Mr Nitecki and colleagues (*Br J Surg* 1993; **80**: 18–20). We find the management rationale of the appendiceal mass presented logical and easily applicable. However, we feel that the role of the interventional radiologist can be fulfilled by the use of ultrasonography alone and that computed tomography has little further to offer. The quoted figure that over 80 per cent of patients who have recovered from an appendiceal mass will subsequently not require elective appendicectomy must be regarded as speculative, and we would urge caution. As military surgeons we are aware that our patients may be sent to remote locations under demanding conditions. Since the number of patients who will suffer recurrent appendicitis cannot be predicted, a policy of elective interval appendicectomy 2–3 months after presentation of an appendiceal mass is offered to all service personnel. This argument could also be applied to other people who travel extensively. Finally, it should be remembered that malignant caecal tumours are not confined to patients over 40 years old, and that delayed diagnosis of these tumours and other conditions will occur if interval appendicectomy is omitted.

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Letter 2

Sir

As a surgeon in training, I read with interest the recent Review on management of the appendiceal mass by Mr Nitecki and colleagues (*Br J Surg* 1993; **80**: 18–20). The authors' recommendation was initial conservative treatment with ultrasonographic or computed tomographic imaging and percutaneous drainage of an abscess, and not the routine use of interval appendicectomy. In my experience, I have not found this to be a satisfactory treatment regimen. First, radiological imaging and drainage have not generally been available out of hours, particularly at weekends. Second, in eight patients receiving conservative treatment, five failed to respond, thus requiring operation. Two patients returned within 1 month with further symptoms requiring operation and only one returned for interval appendicectomy at 2 months. By contrast, in five patients in whom I undertook early surgical intervention, I was able to perform appendicectomy without undue difficulty through an average-sized incision with only one wound infection as a complication. Hospital stay was $\leqslant 6$ days in these patients, a period shorter than or equal to that in those undergoing initially conservative treatment.

I would therefore suggest that, in centres without an active interest in conservative management of the appendiceal mass, early surgery appears to be a safe and effective treatment with minimal hospital stay and inconvenience to the patient.

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Evaluation of routine upper digestive tract endoscopy before laparoscopic cholecystectomy

Sir

We read with interest the article by Dr Ure and colleagues (*Br J Surg* 1992; **79**: 1174–7), in which it was concluded that routine endoscopy is neither clinically useful nor cost-effective in patients with symptomatic gallstone disease. We wish to raise two points about this study.

First, the endoscopic findings in the upper digestive tract among 376 patients before laparoscopic cholecystectomy are reported without division of this population into age classes. The population studied was clearly not homogeneous, patients ranging from 18 to 87 years of age. It would have been interesting to see whether a rising incidence of positive endoscopic findings coexisting with cholelithiasis was associated with increasing age. A recent paper[1] advocated a policy of open-access endoscopy in patients older than 45 years with dyspepsia, anaemia or other non-specific abdominal symptoms. This attitude would translate into higher detection rates of early gastric cancer and, therefore, into better survival rates for gastric malignancy which can obviously coexist with cholelithiasis.

Second, in the paper of Ure and associates, 14 patients were reported to have endoscopically diagnosed peptic ulcers, gastric in eight and duodenal in six. All these patients were treated with the same standard medical therapy, namely omeprazole and colloidal bismuth subcitrate orally, but no reason is given for this medical regimen. Was any test for *Helicobacter pylori* performed? An upper digestive tract endoscopic examination with no signs of peptic ulcer or other organic disease and no test to detect *H. pylori* should not be defined as 'negative'. *H. pylori* is significantly associated with functional disorders of the upper digestive tract, such as non-ulcer dyspepsia[2], which can also cause symptoms similar to those of gallstones. Surprisingly few surgeons take this organism into any account in their practice. We feel that this attitude should be changed and that tests to detect *H. pylori* (biopsy urease test, associated with enzyme-linked immunosorbent assay serology, histological stains, culture or labelled-urea breath test) should be performed on all patients undergoing gastroscopy, even in a surgical department. For patients who harbour *H. pylori*, an appropriate combination therapy of colloidal bismuth, omeprazole and/or antibiotics should be administered.

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A. Tocchi

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1. Sue-Ling HM, Martin I, Griffith J *et al.* Early gastric cancer: 46 cases treated in one surgical department. *Gut* 1992; **33**: 1318–22.
2. Talley NJ, Phillips SF. Non-ulcer dyspepsia: potential causes and pathophysiology. *Ann Intern Med* 1988; **108**: 865–79.

Intrahepatic cholangiogastrostomy for malignant biliary obstruction at the hilum

Sir

I read with interest the Surgical Workshop by Dr Ramesh (*Br J Surg* 1992; **79**: 1349–1350) in which he presents the intrahepatic cholangiogastrostomy as an original modification of the Longmire and Sandford operation described in 1948. The technique reported by Dr Ramesh is not original but has been described by Professor A. M. Dogliotti, formerly of the department of surgery of the University of Turin, in the French[1] and German literature in 1951 and in the English language literature[2] in 1954.

The two techniques for draining the left biliary system after resection of the peripheral part of the liver, using either the jejunum or the stomach, are currently known in the hepatobiliary literature as Longmire–Dogliotti procedures.

At the department of surgery of the University of Turin, the Dogliotti procedure was applied in 20 patients between 1946 and 1972 with two deaths. One of the major complications of this technique not mentioned by Dr Ramesh is the risk of cholangitis from acid reflux into the biliary system (15 per cent in our series). At present we have abandoned the procedure in favour of the ligamentum teres approach to the left duct and segment III duct.

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1. Dogliotti AM. Gastro-intrahepato-ductostomie dans les traitment chirurgicale des obstructions des voies biliaires. *Lyon Chirurgicale* 1951; **46**: 353–6.
2. Dogliotti AM, Fogliatti E. Operation for fibrous stenosis of the common bile duct. *Surgery* 1954; **36**: 69–79.

Author's reply

Sir

In reply to Dr Morino's letter, I wish to make three points. First, there is no mention in my paper that the technique described was original. Second, whenever the biliary system is drained to a portion of the bowel *in continuity* (without Roux-en-Y anastomosis), there is a significant risk of cholangitis similar to the figure described in Professor Dogliotti's series. It is difficult to implicate acid as the cause for cholangitis and death. Following the Longmire operation, cholangitis could also result from other causes such as obstruction and infection in a segment of the liver (usually the right lobe) that is not being drained by the cholangioenteric anastomosis. Third, cholangiogastrostomy is specifically indicated in situations in which a segment III bypass may be difficult, as in patients with bulky subhepatic disease or gross left liver hypertrophy.

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Book reviews

Varicose Veins and Related Disorders

D. J. Tibbs (ed.). 282 × 224 mm. Pp. 576. Illustrated. 1992. Oxford: Butterworth–Heinemann. £150.

This is a big book on one of surgery's Cinderella topics. David Tibbs has had a major interest in varicose veins for many years and is able to bring a whole career's experience to the subject. Along with contributions from his radiological and dermatological colleagues, he has created the most comprehensive yet readable textbook on varicose veins that it has ever been my pleasure to read.

The first part of the volume is devoted to recognition of normal and abnormal, patterns of abnormality, and pathophysiology and its consequences. The scientific groundwork having been laid before the reader, the author continues with chapters devoted to the treatment of varicose veins; everything from microinjection of intradermal venules to vein and valve reconstruction is covered in depth. Finally, there are chapters devoted to the various techniques of assessment that are now available to vascular surgeons and radiologists.

Varicose veins and venous pathology in general have been rather neglected by most general surgeons; nevertheless, it is general surgeons who are called on to deal with the vast majority of varicose veins (at least in the UK). This book can be recommended not only to vascular surgical specialists but also to their more generalist colleagues; it is one of those rare texts that is not only a good read but also a fine reference work.

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Minor Surgery: A Text and Atlas. 2nd ed.

J. S. Brown. 278 × 218 mm. Pp. 326. Illustrated. 1992. London: Chapman and Hall. £55.

This book feels good. It looks good too, and there are many gems of interest, not only for general practitioners who may wish to participate in minor surgery, but also for junior surgical trainees. The book is beautifully illustrated, the text well organized and the combination of writing, lists and diagrams makes for very easy reading.

Dr Brown is right to be cautious about what constitutes minor surgery and describes very clearly the need for appropriate facilities as regards equipment and anaesthesia. He rightly emphasizes the importance of instrument packs, but I wonder how many surgeries would wish to keep a reasonable supply of five different packs. Presumably this is why he also emphasizes the importance of careful planning of lists and audit of activity. The author is right also to confirm that careful histology is obligatory, if only to ensure adequate excision of the lesion. It would have been wise to describe lesions for which more specialist referral might be appropriate.

Most of the areas for injection or aspiration of joints are well described. There may be some practices where tapping abdominal ascites and pleural effusions is appropriate, but I would not wish these to become widespread when more expert care and alternative methods of treatment may be better for the patient. Many of my anaesthetic colleagues might question the sense of caudal epidural anaesthesia or even of Bier's block being part of general practice.

From the surgical point of view the techniques described are very satisfactory and it is right to draw practitioners' attention to the fact that Langer's lines are not always the ones to follow, especially on the face. I am not sure that many patients would like to have a scalp wound closed by knotting a few strands of hair as shown in Figure 11.3, and I have never had to use a hypodermic needle to help suture a wound. On a more serious note, to persist in using silk for skin sutures is now outdated.

The overall quality of this book is such that it can be commended to all practitioners who wish to undertake minor surgery and to junior surgical trainees, who will have to look far to find such wisdom over such a wide range of topics.

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Plastic Surgery Review

A. R. Shons and R. M. Jensen (eds). 278 × 213 mm. Pp. 399. Not illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US $65.

Shons and Jensen's *Plastic Surgery Review* is written in a question and answer form suitable for those wishing to revise for board examinations; it will be useful to those planning to sit the Plastic Surgery Fellowship exams of The Royal College of Surgeons, but would be of limited value to the tyro. It is written by two authors and a number of invited contributors, including some from other specialties whose breadth of experience widens the appeal of the book. It covers the whole spectrum of plastic surgery but has one or two inconsistencies in that some sections are sketchy while others, especially on hand surgery, are very detailed. The main thrust of the book is towards the science and background of plastic surgery and it does not deal with the actual practice of the specialty. In many sections only one approach is described with little mention made of procedures outside the personal preference of the particular writer of the test-type questions. The answers to the questions give reasoned arguments for the correct response, but in some instances errors have crept in. Because of its format this is not suitable as a reference book for those wishing to carry out specific plastic surgery procedures.

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Descent of the Testis

J. M. Hutson and S. W. Beasley. 240 × 160 mm. Pp. 187. Illustrated. 1992. Sevenoaks, Kent: Edward Arnold. £45.

This is a short, clearly written book, illustrated with simple line drawings and good-quality black and white photographs. Chapters 1–3 are a summary of scientific research on the hormonal aspects of descent of the testis and represent an attempt by the authors to dismiss the theory that this process is related simply to androgens. A strong argument, based mostly on work in the authors' department, is proposed to suggest that descent occurs in two phases: (1) abdominal, related possibly to gubernacular swelling and Mullerian inhibiting substance; and (2) inguinoscrotal, related to testosterone action on the genitofemoral nerve with release of second messengers that influence migration of the gubernaculum. One messenger, identified by the authors, may be the calcitonin gene-related peptide. Chapters 4–9 cover the clinical aspects of diagnosis, operative treatment, hormonal management and complications of the undescended testis. This section is not original but provides an up-to-date review of the subject with good references. The final chapter is an overview but somewhat repeats the book's contents. *Descent of the Testis* is a well produced, informative and short volume suitable for surgeons in training; it also provides an excellent overview of the subject for those with an interest in this common problem.

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Dysphagia: Diagnosis and Management. 2nd ed.

M. E. Groher. 240 × 160 mm. Pp. 349. Illustrated. 1992. Oxford: Butterworth–Heinemann. £40.

This is an unusual but important book. Most surgical gastroenterologists think of dysphagia as an oesophageal issue, but many people have neurological problems that interfere with swallowing. It is these that are the main subject matter of this book. The disorders are common, potentially fatal, and often neglected. The author is an ear, nose and throat surgeon who emphasizes close collaboration with other specialists, particularly speech therapists and dieticians. This is the second edition and a small section on oesophageal dysphagia has been added for completeness.

I did not find this book an easy read, but there are excellent chapters on the clinical and radiological assessment of swallowing disorders, and on methods of management by speech therapists and nurses. The only thing that is missing is a formal discussion of the major ethical issues that can arise with this group of patients.

This volume should encourage a more methodical approach to an unfortunate group of patients. It needs to be widely read by neurologists, geriatricians, otorhinolaryngologists, speech therapists, radiologists and nurses. Regrettably, the uninformative title may mean that it is more likely to gather dust on gastroenterologists' bookshelves.

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Clinical Anatomy. 8th ed.

H. Ellis. 244 × 173 mm. Pp. 456. Illustrated. 1992. Oxford: Blackwell Scientific. £22·50.

This is now the 8th edition of this highly successful textbook of clinical and applied anatomy for clinical students; the first edition was published in 1960 and the volume has become an increasingly popular work. The current edition continues the aim of discussing anatomy in the context of clinical examination, radiological investigation and pathological processes. The text and figures for this new edition have been extensively revised; there are many new illustrations.

Each section begins with surface markings of underlying important anatomical structures and follows with the detailed clinical anatomy. The thorax, abdomen and pelvis, upper and lower limbs, and head and neck are covered, and there is a large chapter on the central nervous system. The last chapter, particularly, has been extensively revised. Overall, the book is well laid out. Many of the illustrations contain colour, adding to their clarity.

A minor criticism is that the computed tomograms reproduced sometimes lack clarity, e.g. Figure 188 on page 285. In the next edition further attention should be given to such scans and, in addition, illustrations of some magnetic resonance images would be appropriate in the 1990s.

Apart from these minor detractions this is an excellent text that has a place in medical libraries and on the bookshelves of most students of clinical medicine. Indeed, it would be a welcome addition to the bookshelves of junior doctors and their teachers. The curriculum for students of medicine will change in many universities over this decade, but I have no doubt that this book will remain a favourite with students and teachers alike.

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Atlas of Duplex Scanning: Extremities

J. J. Cranley. 267 × 190 mm. Pp. 414. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US$140.

This second volume addresses the more complex diagnoses of venous, arterial and related disease of the extremities. Five of the seven chapters deal with venous disease. More reliance is placed on the real-time image and venous compressibility and less on Doppler ultrasonography. The illustrations are for the most part convincing, but the reader is left somewhat frustrated at seeing only the 'stills' and having to imagine real-time motion as well as the Doppler signal. Duplex imaging has all but replaced the traditional 'gold standard' of venography for diagnosis of venous thrombosis except in less accessible sites, such as behind the clavicle. Unfortunately, diagnosis and mapping of incompetent perforators and assessment of the saphenopopliteal junction in varicose veins are conspicuous by their absence from this book. The section on differential diagnosis of lumps and bumps, such as popliteal synovial cyst, abscess in the neighbourhood of large vessels in drug abusers, haematoma, lymphadenopathy and lymphoedema, provides a quick means of obtaining the diagnosis in difficult clinical situations. The material in the *Atlas* was obtained before the introduction of digitized instruments capable of greater flexibility and colour-code capacity. Nevertheless, the final chapter on arteries and graft imaging gives some illustration of colour duplex images of aneurysm, pseudoaneurysm and graft occlusion. The more difficult area of critical graft stenosis, however, is not dealt with. This book gives a kaleidoscopic insight into a technique that will replace not only many invasive methods but also some of the less sophisticated real-time imaging techniques over the next decade.

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Surgery: Scientific Principles and Practice

L. J. Greenfield, M. W. Mulholland, K. T. Oldham and G. B. Zelenock (eds). 282 × 220 mm. Pp. 2208. Illustrated. 1992. Philadelphia, Pennsylvania: J. B. Lippincott. £92.

Reviewing a book of this size is a daunting and at the same time rewarding task as this is an authoritative and easily read account of the scientific principles and practice of surgery. The book comes from Professor Greenfield's department in Ann Arbor, Michigan, and the editors have welded together contributions from 155 authors into a uniformity of style and presentation comparable to that of a single-author work. The contributors are drawn entirely from the medical schools of the USA, one-third of them from Ann Arbor. There are many household names but also many younger authors who are active contributors in their fields.

Part I of the book is devoted to surgical principles and sets out the scientific basis of surgical practice, without which surgeons would be in danger of becoming surgical technicians. Some parts of this section will be more readable for the fellowship candidate than the practising surgeon.

Part II, which occupies three-quarters of the book, is a systematic and comprehensive account of surgical practice. Each section starts with a concise account of the anatomy and physiology, and proceeds to a clear description of clinical practice, well illustrated with a uniform style of graphs, tables and line drawings. Surgical technique is succinctly described but it is mostly inadequate for the trainee wanting a full account of how to perform an operation.

This book should be in every library. It should be studied by the FRCS student and read selectively by every practising surgeon who wishes to keep abreast of scientific surgery.

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Notices and announcements

19–24 July 1993
Second United European Gastroenterology Week
Barcelona, Spain
Information: Professor J. R. Malagelada, Calle Calvet 55–57, 08 021 Barcelona, Spain

5–8 August 1993
First Asian Pacific Congress of Endoscopic Surgery
Singapore
Information: Maggie Phang, Congress Secretariat, Conference and Exhibition Management Services, 09-43 World Trade Centre, Singapore 0409

11–14 August 1993
27th Malaysia–Singapore Congress of Medicine
Kuala Lumpur, Malaysia
Information: Organizing Committee, Level 5, MMA House, 124 Jalan Pahang, 53 000 Kuala Lumpur, Malaysia

22–28 August 1993
35th World Congress of Surgery of the International Society of Surgery
Hong Kong
Information: Scientific Secretariat, c/o ISS/SIC, Hauptstraße 63, PO Box 411, CH-4153, Reinach BL 1, Switzerland

27–29 August and
30 August to 2 September 1993
Second International Conference of Gastroenterology
Hong Kong and Chengdu, China
Information: Conference Secretariat, Room 1611-13, World Finance Centre, North Tower, Harbour City, Kowloon, Hong Kong

1–3 September 1993
4th International Congress – International Organization for Statistical Studies on Diseases of the Oesophagus
Paris, France
Information: Michele Liegeon, 2 Boulevard de Montparnasse, 75 015 Paris, France

2–4 September 1993
Second International Workshop: Inflammatory Bowel Disease
Treviso, Italy
Information: Dr G. Di Falco, Divisione Chirurgica III, Ospedale Regionale Generale 'Ca' Foncello', 31 100 Treviso, Italy

3–4 September 1993
Recent Developments in Immunology: Potential Clinical Impact on Surgery and the Treatment of Infection
Würzburg, Germany
Information: Professor A. Thiede, Josef-Schneider-Straße 2, W-8700 Würzburg, Germany

7–10 September 1993
6th International Congress on Interventional Ultrasound
Copenhagen, Denmark
Information: Dr C. Nolsøe, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

10–11 September 1993
Frontiers in Transplantation and Medical Treatment of Liver Disease
Hamburg, Germany
Information: Marion Schemnitzer, Master-Media GmbH, Bodelschwinghstraße 17, D-2000 Hamburg 63, Germany

14–17 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

15–17 September 1993
Nottingham European Organization for Research and Treatment of Cancer Joint Breast Cancer Meeting
Nottingham, UK
Information: Mrs Wendy Bartram, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

29 September to 1 October and
2 October 1993
Principles of Colon and Rectal Surgery, and Biofeedback for Pelvic Floor Disorders/Endorectal Ultrasonography
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue South-east, Minneapolis, Minnesota 55414, USA

17–23 October 1993
Surgery of the Liver, Biliary System and Pancreas
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

18–19 November 1993
Vascular Surgical Society of Great Britain and Ireland Annual Meeting
Manchester, UK
Information: Mr P. L. Harris, VSS Secretary, Link 8c, The Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

30 November to 2 December 1993
Eighth International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr S. C. S. Chung, Combined Endoscopy Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

23–28 January 1994
18th International Congress of Radiology
Singapore
Information: 18th ICR '94, Kent Ridge, PO Box 1052, Singapore 9111

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, 12 203 Berlin, Germany

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Cleveland, Ohio 44 195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians-Universität Munich, Klinikum Großhadern, Chirurgische Klinik, Marchioninistraße 15, D-8000 Munich 70, Germany

20–22 April 1994
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association of Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua do Ouvidor 60/414, 20 040-030 Rio de Janeiro, Brazil

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Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

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The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 500 words, with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

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Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

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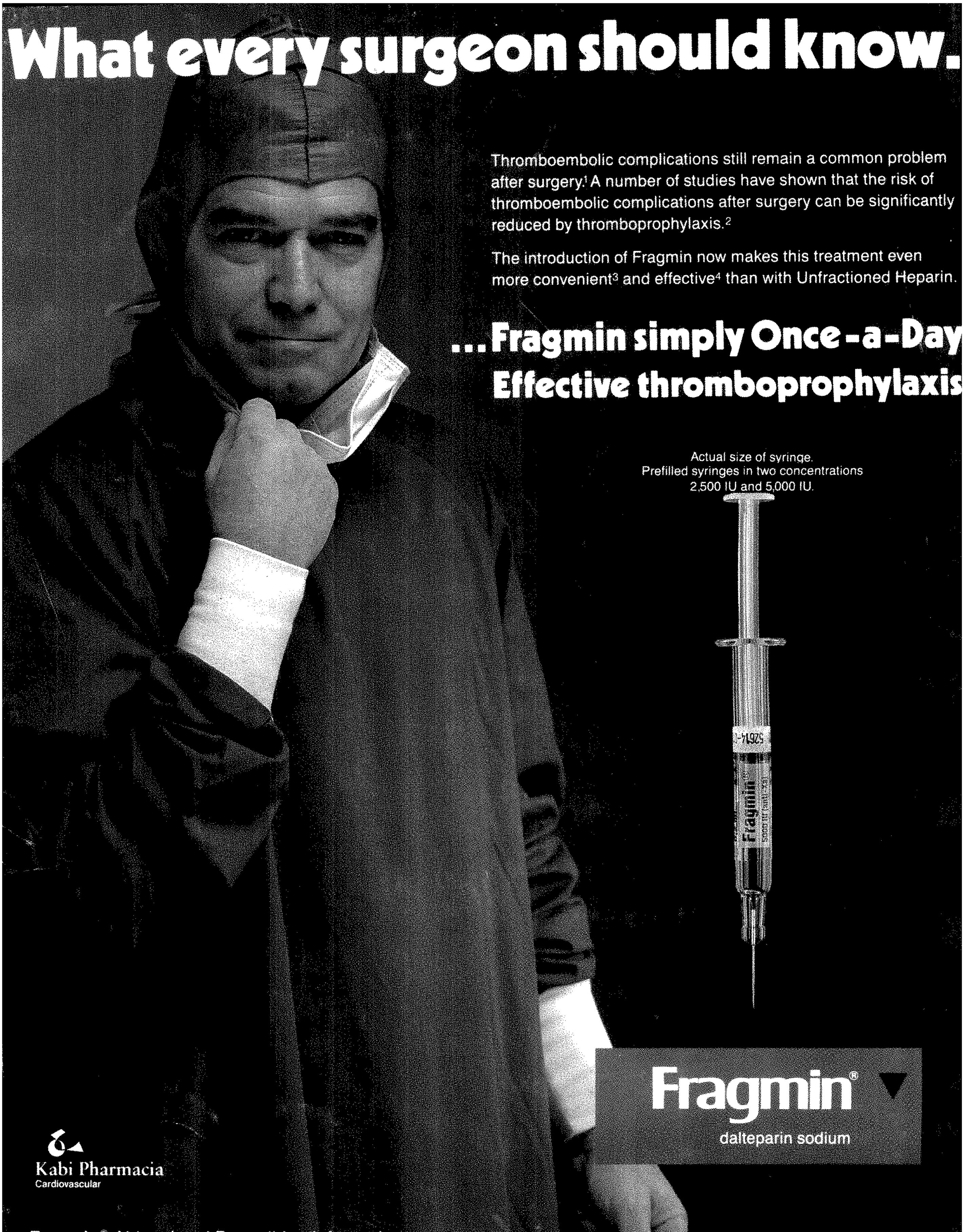

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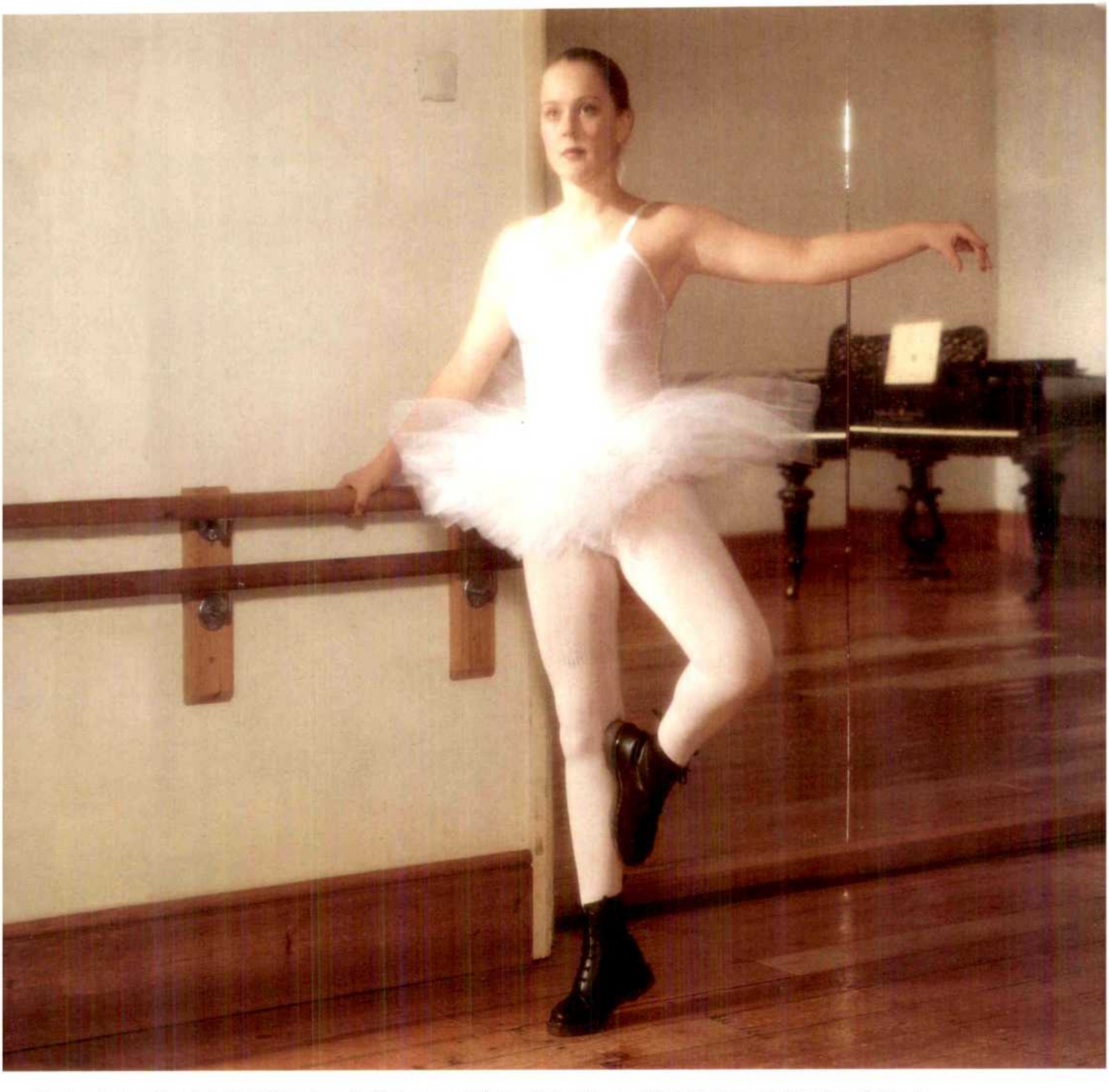

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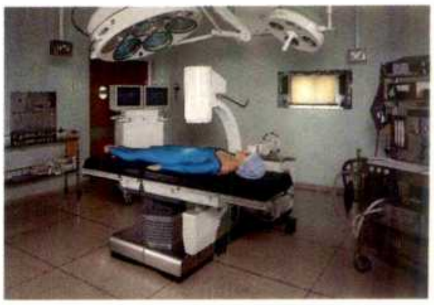

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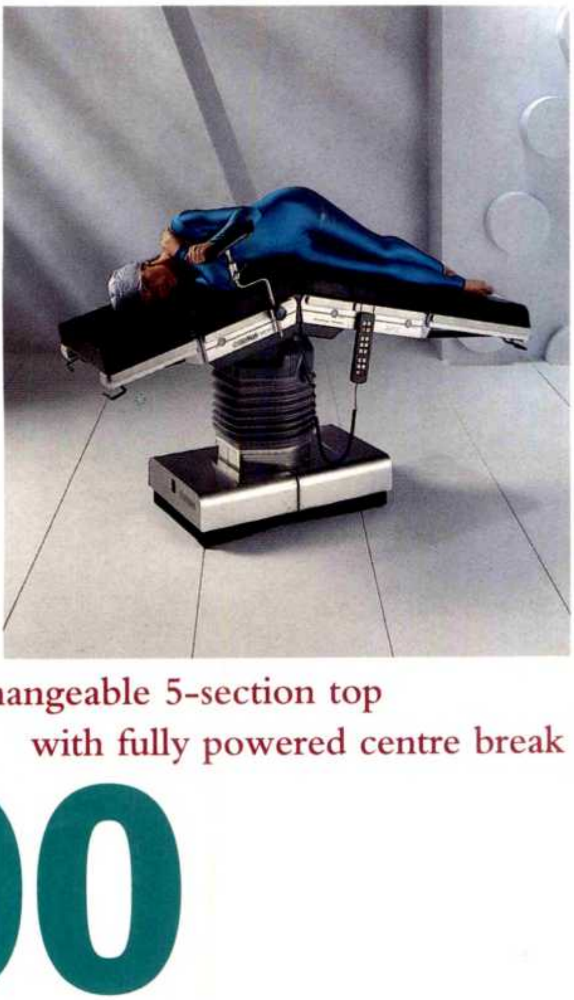

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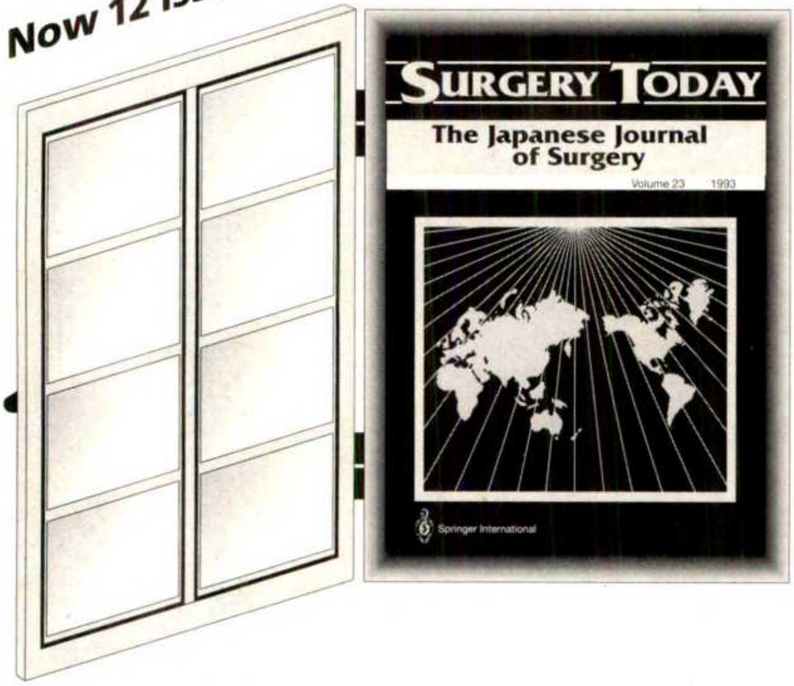

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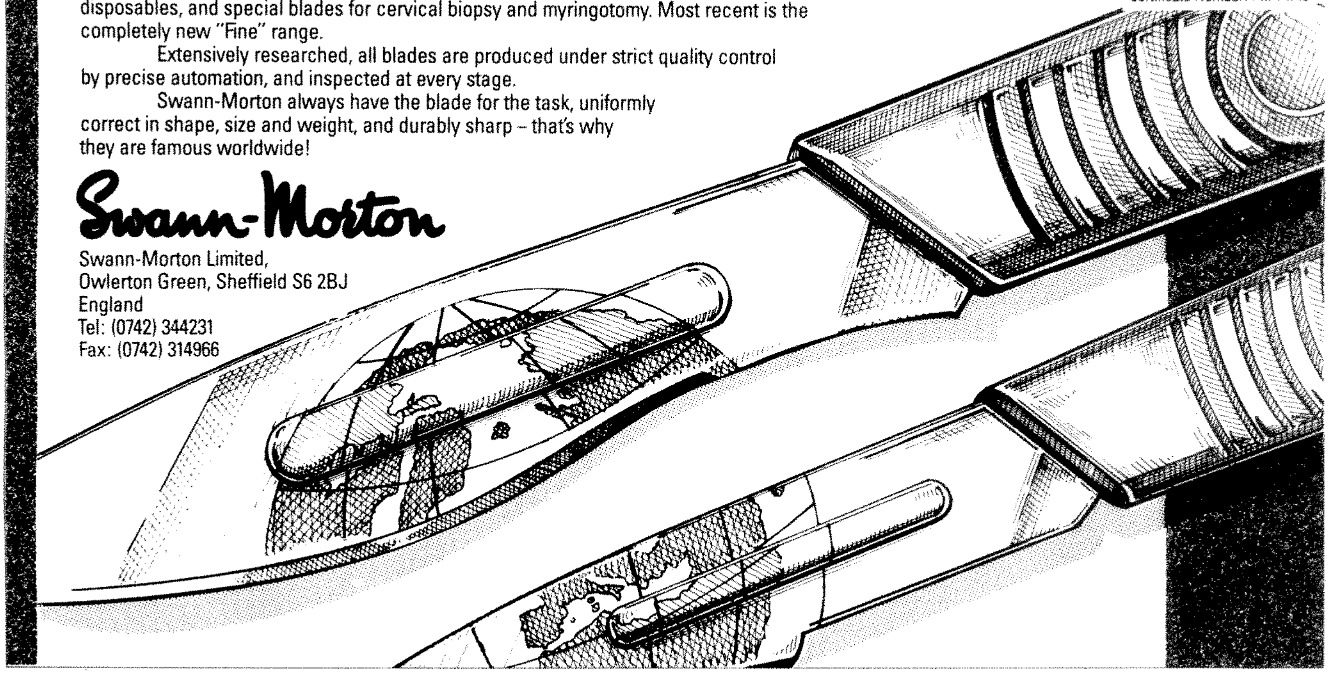

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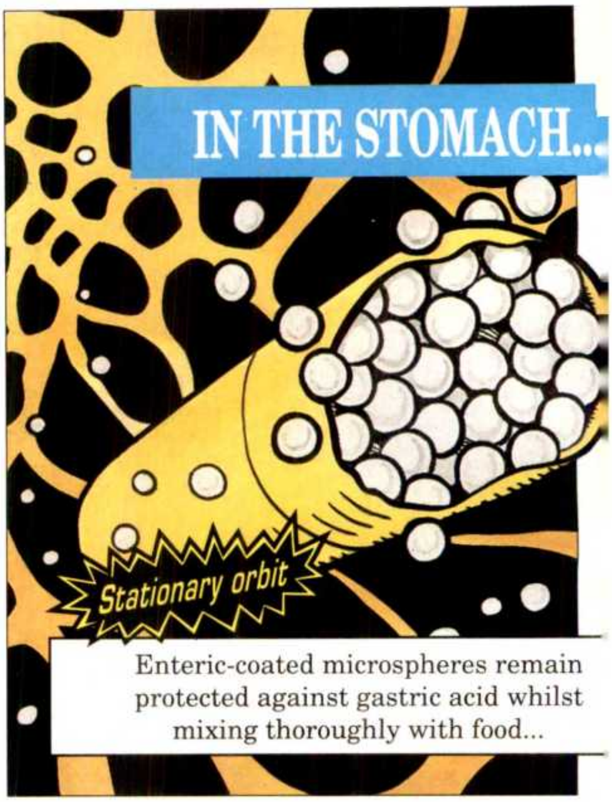

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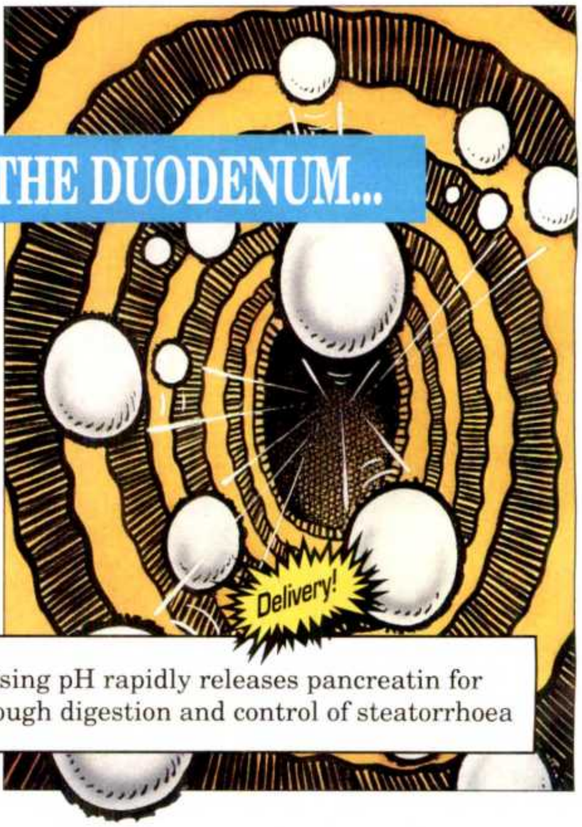
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2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

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he British Journal of Surgery 80th Anniversary

On the 80th anniversary of The British Journal of Surgery, *the Editor looks back at the birth of the Journal in the Summer of 1913.*

r. J. Surg. 1993, Vol. 80,
ly, 817–818

n July 1913 the first number of Volume I of *The British Journal f Surgery* was published under the Chairmanship of ir Berkeley Moynihan of Leeds, with Ernest Hey Groves of ristol as Editorial Secretary. A preamble was written by the en President of The Royal College of Surgeons of England, ickman Godlee, who made an apology for the introduction f the journal because of the 'surfeit of medical literature placed efore the enquiring student', which 'almost destroys his ppetite by its very abundance'. Then, as now, the aims of the ournal were to 'include the best and, as far as may be, only e best, British surgical work of the day'. Today the *BJS* eceives and publishes the best work concerning surgery from nywhere in the world.

Hey Groves, as the first Editor, successfully led the Journal ntil his retirement in 1941. He had 'a natural instinct for iscovering weak spots and could use the blue pencil with firm ssurance'. The sequence of Editorial Secretaries or Editors nce 1941 has comprised Cecil Wakeley (1941–1972), Felix astcott (1972–1978), Crawford Jamieson (1978–1986), and hristopher Russell and David Carter (1986–1991), before the urrent quartet took up office. There is a reduction in the uration of the term of office of Editors and a coincident crease in their number with the passage of time. Some xplanation for this phenomenon can be found in the very first olume. Early editions of the Journal described 'visits to surgical linics at home and abroad'. In the first volume between pages 86 and 694 the Journal visited Rutherford Morison in ewcastle upon Tyne. In those days Morison and his senior onorary surgeon had 42 beds for adults and six children's cots nder their care. In 1913, 8457 surgical operations were carried ut. Mr Morison attended the infirmary every weekday except Vednesdays and operated on Tuesdays, Saturdays and ometimes Thursdays. He taught students on Mondays or ridays. There is no mention of divisional, directorate or dministrative duties in his timetable. The operating list on the ay of the visit included an inguinal herniorrhaphy, repair of ruptured semilunar cartilage and of a fractured patella, astroenterostomy for active pyloric ulceration, exploration for allstones and wide local excision of a malignant lesion of the p with block dissection of the neck. Were these the halcyon ays of surgical practice?

In the first issue are to be found excellent biographical ketches of Joseph Lister (page 3), John Hunter (pages 53–154), Sir Astley Paston Cooper (pages 341–342) and John bernethy (pages 549–550). The Editor of the Journal ontributed a 63-page article on 'Operative treatment of ractures'. The editorial team would not allow themselves, or nyone else for that matter, to receive so many pages these ays! The article was seminal and an example of scientific nquiry, taking a clinical problem to the laboratory and ttempting to understand the mechanisms of fracture repair. nternal and external splints were studied in fractures of the at tibia. The external fixation devices (reproduced as *Fig. 311*) ear an uncanny resemblance to currently used steel work. Vould that the same could be said for anaesthetic equipment. r Robert Kelly from Liverpool on pages 90–95 described the echnique of intratracheal anaesthesia. The motor, blower and nodified anaesthetic apparatus are reproduced as *Fig. 57*. The echnique was used successfully in patients undergoing xploration for cerebellar tumours, removal of the upper or ower jaw, excision of the tongue, thyroidectomy, mastectomy, astroenterostomy, cholecystostomy and cholecystectomy, ileosigmoidostomy, appendicectomy, hernia repair, excision of the rectum, nephrectomy and amputation. In the series described by Dr Kelly 'there was no fatality referable either to the anaesthetic or its method of administration'. Perhaps our colleagues in anaesthesia are unaware of this simple yet effective apparatus that they might find useful in their practice today.

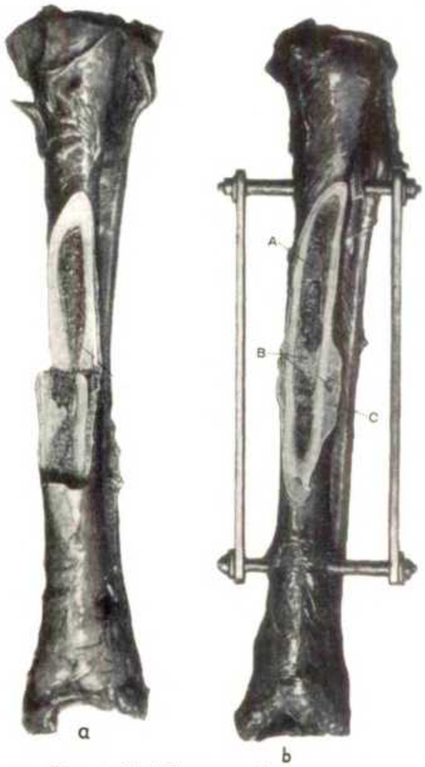

FIG. 311.—CATS' TIBIAS AFTER TRANSFIXION.

(*a*). No. 65, after 7 days. The ends of the bone have a small quantity of blood and granulation tissue between them.
(*b*). No. 57, after 14 days. Early ideal repair. A, Islet of cartilage present in the medulla far from the fracture. B Internal callus present only in the upper fragment. C, External callus.

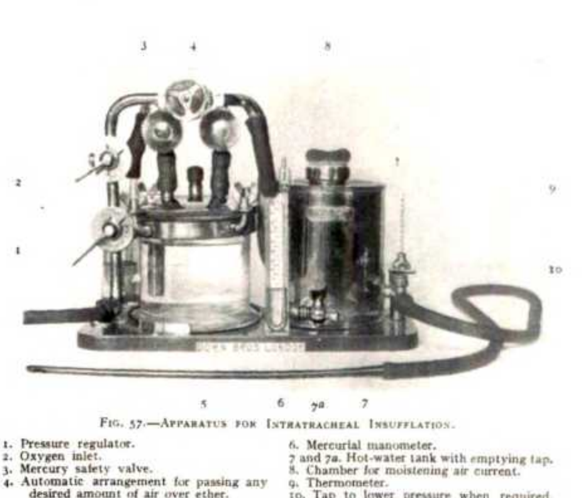

FIG. 57.—APPARATUS FOR INTRATRACHEAL INSUFFLATION.

1. Pressure regulator.
2. Oxygen inlet.
3. Mercury safety valve.
4. Automatic arrangement for passing any desired amount of air over ether.
5. Ether bottle, with arrangement for passing any desired amount of air through ether if required.
6. Mercurial manometer.
7 and 7a. Hot-water tank with emptying tap.
8. Chamber for moistening air current.
9. Thermometer.
10. Tap to lower pressure when required, and connection for tubing.

Size: 15 × 6¼ × 12½ in. high.

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The Journal contained Case Reports, Reviews and notices of books, as it continues to do today. A salutary section was 'Instructive mistakes'. On pages 325–327 are three articles that could relate to today's laparoscopic procedures under the heading 'Wounds of the hepatic and common ducts during the operation of cholecystectomy'.

As the National Health Service hospitals as trusts or directly managed units gradually close down, surgeons can be guaranteed continued work. On pages 145–149 is an article by a Mr Colt from Aberdeen that describes a portable operating theatre. The theatre, 9′6″ long × 5′ wide × 7′ high, is transported on the back of a car or waggon to the patient's home. It was proposed that the car would carry 'in addition to the chauffeur, the surgeon and his assistant, the anaesthetist and a nurse'. The portable theatre would drive to the patient's home, where the chauffeur would carry the patient into the operating theatre, the procedure would be carried out and the patient would then be returned to his or her own bed to recuperate. The portable theatre would ensure appropriate sterile conditions and equipment with adequate operating light. It would prevent soiling the effects of the patient's house and would avoid the unpredictability of facilities when operating in the home.

It is pertinent to review two or three articles that allow some measure of the dramatic change in surgical practice in 80 years. D'Arcy Power wrote on 'Gall-stones'. Cholecystectomy was rarely performed, and the procedures carried out in the 90 patients described were mainly cholecystotomy or partial cholecystectomy. Twenty-three patients died; clearly there have been improvements over the years. The Journal was demanding of statistical methods 80 years ago, and in *Table B* on page 32 the analysis of these gallstone operations is described. Kehr's statistics were applied. The meaning of the statistics and their significance is dubious!

Between pages 699 and 717, James Berry reviewed the 'Present position of surgical treatment of exophthalmic goitre'. Some 80 years ago the best form of treatment for Graves' disease was partial extirpation or ligation of the thyroid arteries. 'Ligation of the inferior thyroid artery is not to be recommended, on account of the greater severity and difficulty of the operation' – difficult to understand these days Remember, however, that none of the patients would have had preoperative preparation. Thyroidectomy was carried out 2 times by Berry in 1913. There was only one death, from haemorrhage. Most of the patients underwent right lobe excision only.

The Journal was truly international from its beginnings and Owen Richards wrote on 'Splenectomy in Egyptian splenomegaly' on pages 419–433. The cause of 'Egyptian splenomegaly' was not known at the time. Almost certainly the patients described had schistosomiasis or bilharziasis (*Schistosoma mansoni*). Twenty-four patients were described in whom splenectomy was attempted or undertaken. The procedure was impossible in two patients. There were four operative and two late deaths.

Monsarrat and Williams (pages 173–182) laid the foundations for current understanding of the growth and local spread of rectal carcinoma. Goyder (pages 259–313) reviewed methods of treating cleft palate and gave results in the follow-up of 50 patients undergoing this type of surgery. Morriston Davies (pages 228–258) wrote on 'Recent advances in the surgery of the lung and pleura'. Within 80 years most of the operations described by this author are no longer carried out.

The end of Volume I (page 733) has a 'Short notice describing the transactions of the British Proctological Society The editorial comments:

> 'We greatly doubt whether the formation of such special societies is for the good of surgical science, and we are glad therefore that this new group has already been absorbed by the Surgical Section of the Royal Society of Medicine'.

Machinations and politics of specialist groups were present 80 years ago. Do remember the historical perspective of the science and craft of surgery. What better way to begin a review than to go back to the early volumes of *The British Journal of Surgery*? Many happy returns on the 80th birthday of the Journal.

J. R. Farndon
Editor

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Br. J. Surg. 1993, Vol. 80,
July, 819–820

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Philippus Christoffel Bornman (born 1943) is Professor of urgery in the University of Cape Town at Groote Schuur Hospital. He graduated from Pretoria, trained in South Africa and the UK, became a consultant surgeon at Bloemfontein in 974 and moved to Cape Town in 1977. He is President of the outh African Gastroenterology Society. He is particularly nterested in pancreatobiliary surgery, including diagnostic and therapeutic endoscopy, and the management of portal hypertension.

PROFESSOR ARUN PAUSAWASDI
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Arun Pausawasdi (born 1938) is Dean of the Faculty of Medicine at Siriraj Hospital, Bangkok. He graduated from Mahidol University, Bangkok, in 1962 and trained both there and in Hamburg, Germany. He was successively Instructor (1973), Assistant Professor (1975), Associate Professor (1978), Professor (1983) and Director (1990) at Siriraj Hospital. He is Secretary-General of The Royal College of Surgeons of Thailand and former Vice-President of the Asian Surgical Association. His special interest lies in biliary disease.

DR BO EKLOF
(USA)

Bo Eklof, who was born in Sweden in 1935, is a visiting Professor at the University of Hawaii, a vascular surgeon at the Straub Hospital, Honolulu, and Medical Director of the Straub Pacific Health Foundation. He trained at the University of Lund in Sweden, spending 1 year at Rochester, New York, USA. From 1981 to 1990 he was Professor and Chairman of Surgery at Kuwait University. His interests are surgical education, thromboembolism, venous reconstruction and reperfusion injury.

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DR HANS-ERIC JENSEN
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Hans-Eric Jensen (born 1928) is Head of the First Surgical Department at Kommunehospitalet and Senior Lecturer at the University of Copenhagen. He trained in Copenhagen and was a research fellow at Michael Reese Hospital, Chicago, USA. He was President of the Scandinavian Surgical Society from 1983 to 1985 and President of the CICD Congress in Copenhagen in 1988. His clinical interests are in ulcer disease, particularly parietal cell vagotomy, and colorectal surgery.

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Attila Csendes was born in Hungary in 1941, moved to Chile in 1949, trained in Santiago and qualified as a surgeon in 1969. After fellowships in Los Angeles, USA, and Aarhus, Denmark, he became Professor of Surgery at the University of Chile in 1982. He held the post of Chairman of Surgery at the University Hospital, Santiago, between 1983 and 1986. His interests lie in gastrointestinal physiology and surgery, notably oesophageal motility, peptic ulcer and gastric cancer.

PROFESSOR ARTHUR LI
(Hong Kong)

Arthur Kwok Cheung Li (born 1945) was educated in Hong Kong and England, graduating from the Middlesex Hospital, London, in 1969. He trained in Cambridge, London and Boston, and joined the staff of the Massachusetts General Hospital, Boston (1979), and then the Royal Free Hospital, London (1980). In 1982 he was appointed Foundation Professor and Chairman of Surgery at the Chinese University of Hong Kong and the Prince of Wales Hospital, Shatin. Hepatobiliary and oesophageal surgery are among his main clinical interests.

PROFESSOR BASIL GOLEMATIS
(Greece)

Basil Golematis (born in 1929) is Professor and Chairman of the First Department of Surgery at Hippocration Hospital, Athens; he has held this post for the past 12 years. He graduated and trained in Athens, spending 1 year on a British Council Fellowship in London in 1959–1960. In 1989 he was appointed Dean of the School of Health Sciences at the University of Athens. He was President of the Hellenic Surgical Society in 1990–1991. His main interest is in the field of gastrointestinal surgery.

Robin Williamson

Br. J. Surg. 1993, Vol. 80, July, 821–822

Carotid endarterectomy: confidence restored

Few vascular surgical procedures have been debated so much as carotid endarterectomy. Concern was raised previously about the risk of this operation and the scale on which it was being performed: too great in the USA and too small in the UK. The American and European carotid surgery trials have now unequivocally shown the benefits of this procedure for patients with transient ischaemic attack (TIA) or minor stroke and >70 per cent internal carotid artery stenosis on the relevant side[1,2]. These trials have restored confidence in the operation. Concern has shifted from the well known risks of surgery to the unexpectedly high risks of medical treatment alone. Medical therapy results in a rate of stroke or death of 25–30 per cent at 2 years in patients with symptoms and >70 per cent stenosis. There is a clear correlation between risk and degree of stenosis; patients with >90 per cent stenosis are at greater risk of stroke than those with $\leqslant 90$ per cent. Conservative treatment is particularly dangerous when the contralateral carotid artery is occluded; 56 per cent of such patients will experience stroke or death within 2 years compared with 20 per cent of those treated surgically (H. J. M. Barnett, personal communication).

The extent of extracranial obstruction is an important factor in determining the risk of stroke. This includes the status of the vertebral arteries, an often neglected area, which lend themselves equally well to non-invasive investigation as the carotids. Hennerici *et al.*[3] showed, in asymptomatic patients with carotid bruit, that the cerebrovascular risk is sixfold greater when the vertebral arteries are diseased as well as the carotids. The most likely explanation for this is that more extensive disease reduces the availability of a collateral circulation, thereby rendering the brain vulnerable to stroke. One must consider the cerebral arterial system as a whole and not be blinkered by exclusive interest in a single carotid artery. Another part of the system that should not be neglected is the circle of Willis, which connects the carotid and vertebral circulations. Deficiencies in the circle, together with major extracranial obstruction, may increase the risk of stroke. This is most obvious when a carotid artery becomes occluded, either during surgery or when stenosis progresses to occlusion during conservative treatment. Indeed, progression to occlusion is one of the dangers of withholding surgery for carotid stenosis. We have been able to show prospectively that the risk of developing a stroke at the moment of occlusion is about 20 per cent, even when the patient is receiving antiplatelet agents[4]. Furthermore, the risk of stroke remains increased after occlusion. The Extracranial/Intracranial Bypass Study[5], reported in 1985, showed that the annual stroke rate in patients with occlusion treated medically is about 5 per cent. This is higher than the 2 per cent rate that can be expected following prophylactic carotid endarterectomy. Prevention of occlusion is, therefore, important and carotid occlusion should be included as an endpoint of clinical trials comparing various forms of treatment for symptomatic or asymptomatic carotid stenosis. It is not easy to determine whether patients are truly asymptomatic; some may have forgotten symptoms experienced long ago, some may have cerebral symptoms that are difficult to relate to the carotid stenosis, and some may appear asymptomatic but have so-called 'silent' infarcts on computed tomography or magnetic resonance imaging of the brain. Whether carotid endarterectomy should be performed for assumed asymptomatic stenosis is currently under investigation; an answer will come from randomized trials within the next few years. One recently published trial on a limited number of 444 asymptomatic patients has provided some insights[6]. Carotid endarterectomy reduced the incidence of neurological events, i.e. TIA and stroke. There were 17 (8·0 per cent) ipsilateral events in patients undergoing surgery and 40 (20·6 per cent) in those given medical treatment; half of the events were strokes and half TIAs. Carotid endarterectomy did not influence the combined incidence of death and stroke, but this was due largely to the high perioperative mortality rate of 1·9 per cent, which was mainly cardiac and not neurological in origin.

To obtain a beneficial effect of surgery for asymptomatic stenosis similar to that for symptomatic disease, it is necessary to identify asymptomatic patients who are at increased risk of stroke. Likely candidates are those with extensive involvement of both carotid and vertebral systems, who have diminished collateral reserve. The most obvious patient has high-grade stenosis on one side and contralateral occlusion.

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Several new diagnostic techniques, such as transcranial Doppler ultrasonography with carbon dioxide inhalation, test the integrity of the autoregulation mechanisms that are necessary to avoid local hypoperfusion. Hypoperfusion in its own right is harmful and it may also render the brain more vulnerable to the effects of embolization. It is probable that there is an interaction between haemodynamic and embolic factors. That diminished cerebrovascular reserve increases the risk of stroke during conservative treatment has been shown prospectively for patients with carotid occlusion[7]. A similar study should be carried out for patients with stenosis and should also investigate prospectively the type of carotid plaque that is likely to lead to embolization. High-resolution ultrasonography can classify plaques. Probable threatening characteristics are ulceration and hypoechogenicity, representing haemorrhage and cholesterol deposition. Intraplaque haemorrhage suggests instability of the plaque and may cause a sudden increase in the degree of stenosis and embolization.

Identification of patients at increased risk of stroke is important, but the key factor in making carotid surgery more widely accepted is a reduction in operative complications. Before operation this should include proper cardiac assessment. During operation adequate cerebral perfusion must be ensured and a technically perfect reconstruction carried out. After operation hyperperfusion must be recognized and avoided. There are many ways of accomplishing these goals, and monitoring of cerebral function makes the surgeon aware of potential problems and helps to avoid them[8]. It is reassuring to know that it is possible to perform the operation with <3 per cent risk of neurological event or death, as shown in the ongoing Asymptomatic Carotid Atherosclerosis Study[9]; the monitoring committee would have stopped randomization if perioperative morbidity and mortality rates had exceeded the anticipated value of 3 per cent and this has not occurred. It should be noted that there was a rigorous selection process for surgeons who wished to participate in the study; choice of the proper surgeon may be as important as selection of the proper patient. The outcomes of the recent carotid surgery trials have restored confidence in this procedure, but this confidence will remain only if the surgical community as a whole can achieve the same results as the surgeons who participated in the trials. This requires continuing regional audit, preferably by neurologists. Similarly, it is essential to audit conservative management – remembering its higher risks – but, sadly, this is not as easy to accomplish as surgical audit. In the Netherlands a review of general practice showed that only one of four patients with TIA is referred for specialist consultation. The situation may be different in other countries, but underuse of a procedure that prevents death and stroke is a major cause for concern.

The old doubts about carotid endarterectomy have made it one of the best evaluated of surgical procedures. It has been shown to be one of the most worthwhile of operations. Carotid stenosis should now be actively sought using ultrasonography and, when found, it should be treated appropriately, including randomization in ongoing studies when necessary. The time for ignoring carotid bruits and prescribing aspirin therapy uncritically is over.

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Br. J. Surg. 1993, Vol. 80, July, 823–824

Recurrent varicose veins: a national problem

Scene: Sister's office, a surgical ward in any National Health Service hospital
Time: Coffee time, after the Monday morning ward round
Consultant: 'We had better think about tomorrow afternoon's operating list; I will start with the highly selective vagotomy and follow that with the right hemicolectomy'. (*Turns to newly appointed registrar*) 'Unfortunately, John, I have a management board meeting after that, so perhaps you could finish off with the varicose veins'.
Newly appointed registrar: 'Well, I'm not sure ... I was doing a urology job before this you know ...'
Consultant: 'Oh, I'm sure you don't need me to tell you how to do simple straightforward varicose veins; you must have seen plenty in your time ... '

Only too often, such is the start of the chain of events that ends with the patient's readmission after investigations for recurrent varicose veins, as described by Bradbury and colleagues[1] in this issue. These authors report that, of 1014 consecutive varicose vein operations undertaken in the Lothian Region between 1 January 1990 and 31 December 1990, approximately 20 per cent were performed for recurrent disease. This regrettably high incidence of recurrent varicose veins has also been demonstrated by Sarin and colleagues[2], who collected the results of seven controlled clinical trials comparing the results of saphenofemoral ligation with and without stripping of the long saphenous vein (LSV). When the LSV was stripped, the mean recurrence rate was 18·7 per cent; without stripping it was 35·1 per cent.

Apart from the irritation caused to the patient who must return to hospital for an operation that should have been successful first time around, recurrent varicose veins are a continuing burden on waiting lists, particularly those of vascular surgeons who are known to take an interest in the problem. Recurrent varices must significantly decrease the cost–effectiveness and efficient running of NHS surgical wards; how can we improve this state of affairs? I suggest that this is neither difficult nor time consuming; appropriate action may be described under two headings – 'attention to detail' and 'supervision'.

The most common cause of recurrent varicose veins is an inadequate initial operation with failure to perform a flush saphenofemoral ligation with ligation and division of all tributaries[3–8]. This is often due to an inadequate incision, which is also the usual reason for the serious complications of long saphenous surgery, namely trauma to the femoral vein or artery. The importance of accurate adequate access cannot be overemphasized. Before flush ligation of the saphenofemoral junction (SFJ), the femoral vein must be confidently identified through the cribriform fascia. Failure to do this is likely to mean failure to ligate one or more tributaries (or even the saphenous vein itself), which will lead to recurrent varices.

Controversy continues about whether or not to strip the LSV, but evidence is growing that limited stripping, from groin to knee level, gives better results than simple flush ligation of the SFJ alone[2]. Sarin and colleagues used duplex ultrasonography to investigate reflux in the LSV after saphenofemoral ligation, with and without stripping to below the knee. SFJ ligation alone resulted in a 45 per cent incidence of LSV reflux in the calf, compared with 18 per cent after ligation and stripping. In most cases the source of this reflux is a persistent mid-thigh (Hunterian) perforating vein; Sutton and Darke[9], using descending saphenography, demonstrated at least one mid-thigh perforator in 87 per cent of 80 saphenograms. Limited stripping of the LSV, to knee or upper-calf level, minimizes the risk of damage to the saphenous nerve[10] and the argument that stripping the LSV 'destroys the body's most important spare part' is denied by most cardiac surgeons, who dislike using the varicose and dilated thigh segment of the saphenous vein for coronary artery bypass.

Recurrence involving the short saphenous vein (SSV) is a less common problem than that involving the long saphenous system, but only because short saphenous incompetence itself is less common. Much inadequate surgery is done in the popliteal fossa, often due to lack of appreciation that the SSV lies beneath the popliteal fascia and failure to divide this invariably leads to recurrence. Accurate identification of the saphenopopliteal junction is essential. Where a duplex scanner is available, this is the simplest and most accurate method; otherwise short saphenous varicography or, less accurately, hand-held Doppler ultrasonographic examination, is essential.

Considering supervision, those who undertake varicose vein surgery must be

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prepared to be sufficiently patient to assist their senior house officers and registrars, and to ensure that they are thoroughly competent before undertaking these simple but error-prone operations on their own. Regrettably, the present shortage of operating theatre time in most hospitals in the UK and pressure to keep waiting lists down are not conducive to the unhurried surgery that is essential for such teaching.

Does day-case varicose vein surgery result in a higher incidence of recurrence? I know of no evidence that this is so. Day-case surgery should affect only the length of time that the patient is in hospital, not the technique of the operation. Indeed, day-case surgery is more likely to be undertaken by consultants or experienced senior registrars and so it might be expected to have a lower rate of recurrence than those many operations that are undertaken by inexperienced unsupervised senior house officers or registrars at the end of an inpatient operating list.

Varicose vein operations are the antithesis of glamorous surgery. They do, however, provide a useful and widely available training ground for teaching young surgeons the importance of careful observation and dissection early in their careers. A little more attention to this aspect of training and, indeed, a little more attention to detail by some trainers, should vastly improve the recurrence rate and thus the cost–effectiveness of these common operations.

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Infrainguinal vein graft stenosis

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Although knowledge of the biological processes involved in the development of intimal hyperplasia has increased markedly in recent years, the precise aetiology of infrainguinal vein graft stenosis remains undetermined. Current therapy is therefore directed at treatment of the established lesion rather than its prevention. There seems little doubt, however, that recent advances in understanding of the vascular biology of normal and pathological saphenous vein will eventually lead to specific targeted therapy that will allow the prevention of vein graft stenosis.

or the majority of patients with critical lower-limb ischaemia, ypass grafting is the treatment of choice. Autogenous phenous vein is the most commonly used infragenicular onduit and provides patency rates of 60–85 per cent[1–5] at 2–5 ears. Most of the grafts that fail between 1 and 12 months do t because of the development of stenosis[6]; close graft urveillance with early secondary intervention is necessary to chieve optimal patency rates. Despite intensive research for ost of the past decade, the aetiology of graft stenosis remains defined. This review examines the history, clinical features nd histopathology of such lesions and considers the current ypotheses regarding their aetiology. Prospects for new herapeutic approaches and prevention are discussed.

History

utogenous saphenous vein was first used to bypass the emoropopliteal segment over 40 years ago. In 1949, Kunlin[7] ntroduced the end-to-side anastomotic technique for reversed ein grafts, which Linton and Darling[8] later adopted with an 5 per cent technical success rate. Reports of stenoses occurring these grafts soon appeared associated with graft failure or a eturn of symptoms[9–16]. Szilagyi *et al.*[17], in 1973, were the first o report a comprehensive study of the changes seen in reversed ein grafts. Using angiographic follow-up data from 260 grafts, wo major types of change were identified: stenotic lesions in 5 grafts (21 per cent), occurring at a mean of 15 months after mplantation, and the later development of atherosclerosis in) grafts (8 per cent) at a mean interval of 45 months. Stenotic sions were subdivided as follows: diffuse intimal thickening 21), fibrotic stenosis (11), fibrotic valve (15) and suture enosis (eight). This classification was based largely on ngiographic appearances as histology was performed in only ine cases. Stenosis adjacent to the anastomosis was generally onsidered to be 'traumatic fibrotic stenosis' following clamp njury; midgraft web-like stenosis was interpreted as valvular, nd ring-like stenosis at the site of tied branches was thought o be caused by sutures. Interest initially centred on valve enosis after animal studies demonstrated that fibrotic egeneration of valve leaflets could produce stenosis[18] and, in series of human reversed vein grafts, ten of 11 stenoses were natomically and histologically confirmed as valvular in origin[19]. However, as experience with angiographic follow-up f grafts grew, fewer and fewer of the stenotic lesions ncountered could confidently be attributed to degenerative alves[20,21]. The precise aetiology of the remaining stenoses was nknown.

At about the same time, *in situ* vein grafting was gaining in opularity, following the demonstration by Leather and olleagues[22] of increased vein utilization and, apparently, uperior patency rates compared with the reversed vein chnique. It was also claimed that *in situ* bypass caused less ndothelial and vein wall injury because of reduced dissection, handling and distension[23–25]. In addition to improving the early patency rate, it was hoped that this would lead to fewer of the traumatic fibrotic stenoses to which Szilagyi and colleagues had referred. An analysis of the incidence of stenosis in several of the series of reversed and *in situ* vein grafts reported to date (*Table 1*) illustrates that this initial hope has not been fulfilled: the incidence of stenosis in the two types of graft is similar. It is now known that the *in situ* technique can produce significant endothelial and smooth muscle cell injury[35,36], and that factors other than vein trauma may be involved in the aetiology of stenosis.

Clinical features

As shown in *Table 1*, approximately 20 per cent of all grafts develop stenosis and nearly 80 per cent of these lesions occur in the first year after surgery. The majority are localized (< 2 cm long)[29,37,38], although a higher incidence of diffuse lesions (2–6 cm long) has occasionally been reported[39,40]. The majority of haemodynamically significant stenoses are associated with neither the development of ischaemic symptoms nor decreased peripheral pulses[32]. Graft surveillance of some form or other is, therefore, necessary to detect these lesions and the relative merits of the various methods of surveillance have recently been reviewed[41].

Few studies have looked in detail at the factors associated with vein graft stenosis. Sladen and Gilmour[20] found no association between stenosis and patient age, sex, presenting symptoms, hypertension, diabetes, smoking and outflow artery. Two interesting trends have been reported by Berkowitz and colleagues[27]. First, the incidence of stenosis is higher in more distal grafts (above-knee, 8 per cent; below-knee, 12 per cent; tibial, 18 per cent). Second, the most common site for stenosis in a reversed vein graft is within 4 cm of the proximal anastomosis (40 per cent)[37]. In one study of *in situ* bypass, stenosis was more common in the distal third of the graft[34]. These results are not contradictory, however, as it is the same distal section of the original saphenous vein that develops these lesions. Small vein diameter has been associated with distal stenosis[34] and a positive correlation between vein calibre and long-term patency rate has been noted[42,43].

Vein grafts develop both anastomotic and intragraft stenosis which, in terms of aetiology, should probably be considered separately. From *Table 1* it can be seen that just over half the stenoses are true intragraft lesions with the remainder occurring at the anastomoses. This contrasts with the situation in prosthetic infrainguinal grafts, in which anastomotic intimal hyperplasia (IH) is the major cause of graft failure[44] whereas intragraft stenosis is rarely seen.

Histopathology

The morphological lesion underlying vein graft stenosis is IH, defined as an abnormal accumulation of cells and extracellular

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Table 1 *Incidence, site and timing of stenosis in reversed and* in situ *saphenous vein grafts*

Graft type	Reference	No. of grafts	Stenosis			Time of stenosis (percentage of stenose in first year)
			Anastomotic	Intragraft	Total	
Reversed	Mills *et al.*[26]	379	26 (7)	24 (6)	50 (13)	—
	Berkowitz *et al.*[27]	521	48 (9)	61 (12)	109 (21)	61
	Sladen and Gilmour[20]	173	10 (6)	23 (13)	33 (19)	66
	Szilagyi *et al.*[17]	260	—	—	55 (21)	—
	Wengerter *et al.*[28]	63	3 (5)	8 (13)	11 (17)	—
	Moody *et al.*[29]	40	—	—	10 (25)	—
	Mean (%)		7	11	19	—
In situ	Wengerter *et al.*[28]	62	4 (6)	6 (10)	10 (16)	—
	Moody *et al.*[29]	34	—	—	8 (24)	—
	Disselhoff *et al.*[30]	48	0 (0)	7 (15)	7 (15)	70
	Bergamini *et al.*[31]	316*	20 (6)	34 (11)	54 (17)	—
	Grigg *et al.*[32]	80	9 (11)	10 (12)	19 (24)	100
	Thompson *et al.*[33]	48	9 (19)	4 (8)	13 (27)	—
	Varty *et al.*[34]	66	7 (11)	11 (17)	18 (27)	88
	Mean (%)		9	12	21	—

Values in parentheses are percentages. *Series of 361 grafts minus early failures, deaths and those lost to follow-up

matrix in the intima of the vessel wall[45]. This appears to be a uniform response in the vasculature to a wide variety of injurious stimuli and is seen after angioplasty[46], endarterectomy[47], embolectomy[48–50], arterial catheterization[51], vein grafting[52–55] and at anastomoses between prosthetic grafts and native vessels[56]. Although the lesions at these various sites are morphologically similar, suggesting a common aetiology, this review focuses on the changes occurring in vein grafts because veins possess a number of unique properties that could influence the development of IH[57].

It is important to note that most saphenous vein grafts are not 'normal' to begin with. The classical textbook description[58] of the structure of the saphenous vein is of a thin intima consisting of the endothelium and supporting connective tissue, a muscular media separated from the intima by a poorly defined internal elastic lamina, and a thick adventitia of loose connective tissue. However, in patients undergoing bypass these features are rarely seen and the majority have some degree of pre-existing intimal thickening and medial fibrosis[52,53,59,60]. Although the term phlebosclerosis has been used to describe these changes, it is not entirely a fibrotic process[61]. The intimal thickening is often highly cellular, containing smooth muscle cells (SMCs) of both contractile and secretory phenotypes[62,63].

The changes seen in vein grafts during the first few weeks after their insertion are largely inflammatory and reparative in nature, the extent depending on the degree of injury sustained during harvesting and implantation. There are areas of endothelial loss, with platelet and fibrin deposition and an accumulation of neutrophils and macrophages within the vein wall[52]. Necrosis of medial SMCs is also seen[64]. Re-endothelialization is generally very efficient[65,66] but persistent gaps between cells have been observed, suggesting that a fully confluent endothelial layer may not be achieved[67]. The time taken for re-endothelialization depends on the extent of the initial loss[52]. Short 1-cm defects can be re-covered in 1 week and 5-cm lengths in 6 weeks. Unless there has been severe endothelial loss, the source of the regenerating cells is from the surrounding vein wall. Disrupted vasa vasora[68,69] are re-established within 1 week, although reinnervation of the vein wall takes 1–2 weeks longer[70].

The mature vein graft develops a thickened intima due to IH, whereas the media is thinned[52,53,57]. This process has been incorrectly referred to as vein graft 'arterialization'. The thickened intima and thin fibrotic non-compliant media of a vein graft bear little resemblance to normal arterial structure. Graft stenosis represents a focal area of excessive IH occurring on top of the background IH seen throughout the graft. These lesions consist of SMCs lying in an abundant stroma of acidi mucopolysaccharide matrix[57]. With maturity, increasin amounts of elastin and collagen are also seen in the extracellula matrix[71]. Electron microscopy of intimal SMCs has shown tha a significant proportion undergoes a change from a contractil to secretory phenotype, with reduced numbers of actin filament and more rough endoplasmic reticulum and Golgi apparatus[56,72]. These ultrastructural features are similar to thos seen in fibroblasts, which were once thought to be the mai cell type in intimal hyperplastic lesions. This has led to som confusion in nomenclature, with stenoses being referred to a 'fibrotic' lesions. Although extracellular matrix and collage formation are important components of the lesion, this term fails to convey the proliferative nature of the problem and th central role played by the SMC. Fibrosis is more prominen in the media[57] of vein grafts following necrosis of SMCs. Th morphological appearances of an anastomotic stenosis are ver similar to those of an intragraft stenosis, with IH at the sutur line, in the heel and toe of the graft, and in the floor of th recipient artery[56].

Aetiology

Investigation of the aetiology of vein graft stenosis demand the use of experimental systems. Animal models of IH hav been the most popular experimental tool but the results of thes investigations, particularly in small animals, have not bee uniformly reproducible in human studies[73]. Cell cultur techniques have been useful for probing the cellular mechanism involved in IH but results need to be interpreted with caution More recently, Angelini and colleagues[74,75] have reported th use of cultured human saphenous vein to study IH; this ma prove to be a valuable experimental tool in the future. Despit these limitations, a coherent picture of the main precipitants cellular elements and mediators involved in the production o IH can be drawn from the experimental work to date.

The vein used as a bypass graft has to be 'disturbed (dissected, handled, distended, cannulated and valves cut) an is then exposed to pulsatile high-pressure and rapid flow Logically, therefore, injury and haemodynamic stress have bee the prime aetiological suspects since stenoses were firs described. Certainly, for anastomotic lesions the evidence i now strong that flow abnormalities are the principal causativ factor. A number of other possible factors have been proposed of these, the pre-existing venous abnormalities discussed abov have recently received most attention.

e-existing venous disease

e morphological similarity between the changes frequently served in the intima of the long saphenous vein and IH seen vein grafts has led to speculation that they may be related[63]. roving this link is difficult, but the results of two recent studies ovide indirect evidence of an association. Panetta and lleagues[76] demonstrated that veins with thickened walls, eas of calcification and recanalized thrombosis had inferior tency rates at 30 months (32 *versus* 73 per cent) when used bypass grafts. Furthermore, the microscopic changes of timal thickening have been shown by Davies and -workers[77] to produce a decrease in vein wall compliance at was associated with a higher incidence of stenosis.

jury

he role of injury in the pathogenesis of IH has been extensively udied in animal models in which angioplasty of the carotid, rta or iliac arteries is used as the injurious stimulus. This oduces de-endothelialization and medial SMC injury[78–81]. carpet of platelets is deposited on the exposed subendo-elium[82] and up to 25 per cent of medial SMCs undergo crosis[83]. After this, 20–30 per cent of the surviving SMCs art synthesizing DNA[80], undergo a phenotypic change[81] and igrate into the intima. These SMCs express messenger RNA nRNA) for tissue plasminogen activator[84], suggesting that asmin, which can degrade a number of matrix molecules and tivate collagenases, may facilitate the migratory process. In eas where endothelial regeneration is rapid, intimal prolifer-ion of SMCs is limited[85] and falls to baseline levels[86] in 8 eeks. Despite this, intimal thickening may still progress for p to 12 weeks after injury owing to the secretion of extracellular atrix by these cells[78]. Paradoxically, although delayed -endothelialization leads to a higher SMC proliferation rate, is does not necessarily produce more IH[87]. If fine catheters e used to remove the endothelium, thereby avoiding medial MC injury, intimal proliferation does not occur[88]. These ndings suggest that a hierarchy of cells is involved in the sponse to injury, with the SMC at the top, followed by the dothelial cell and, lastly, the platelet. The role of flammatory cells arriving in the vein wall in the early phase ter grafting is unclear.

Platelets. The demonstration that inducing thrombocyto-enia in rabbits dramatically reduces IH following angioplasty ggests that platelets play a major part in the pathogenesis of yperplasia[89]. The theoretical grounds for this argument are ow well established: platelet granules release platelet-derived owth factor (PDGF), epidermal growth factor and thrombo-ondin, which act as direct mitogens or facilitate mitogenesis SMCs[90,91]. However, in a more recent study in which rats ere made thrombocytopenic for a short period only using a olyclonal antiplatelet antibody, no reduction in SMC oliferation was seen following carotid artery angioplasty[92]. timal thickness in the first 7 days was, however, reduced, ossibly because of a fall in SMC migration. In human phenous vein the presence of SMCs within the intima before rafting suggests that migration may not be such an important ep in vein graft IH and that platelets may therefore play only minor role in its aetiology. The failure of antiplatelet agents influence unequivocally the development of IH in experi-ental vein grafts or to influence patency rates in clinical studies ems to support this view[93–95]. The demonstration that most the growth factors released by the platelet can be produced y the endothelium and SMC[96–101] illustrates that these cells e capable of taking over the role of the platelet after the initial ief period of platelet deposition at the site of injury[83].

Endothelium. Although localized injury to the endothelium lone in arteries does not produce IH[88], it is not known whether the same applies to vein grafts. The injury to venous ndothelium during grafting is usually quite substantial and -endothelialization takes place in an arterial environment to which the endothelium is not adapted. As indicated earlier, persistent defects may occur in the endothelium, which also becomes functionally abnormal[102–104]. It is possible that in these circumstances the endothelium may act as a promoter of IH rather than as an inhibitor[105]. A 'normal' confluent endothelial layer prevents the development of IH by creating a physical barrier between serum mitogens and the vein wall, and by secreting SMC growth inhibitors such as heparin[106–108] and endothelium-derived relaxing factor[109]. Injured endothelium, on the other hand, can produce a number of SMC mitogens, such as PDGF[99] and basic fibroblast growth factor (bFGF)[110], and no longer fulfils its function as a physical barrier. The role of altered endothelial function in IH requires further study[105].

Vascular smooth muscle cells. The demonstration that in arteries the degree of SMC proliferation is related to the extent and depth of the initial trauma suggests it is the direct SMC injury that is the major determinant of IH[111,112]. The phenotypic change from a contractile to secretory type that these cells undergo is an integral part of the response to injury[80]. The secretion of glycosaminoglycans, elastin and collagen by these cells ultimately produces the main bulk of the restenotic lesion[113]. In canine vein grafts, Quist and LoGerfo[114] recently demonstrated that injury occurring during harvesting resulted in 100 per cent of SMCs undergoing phenotypic modulation to the secretory type, whereas no SMCs in optimally prepared veins did so. The stimulus for these changes may be partly a response to the platelet and endothelial mitogens described above but, in addition, SMCs release their own mitogens to stimulate proliferation in an autocrine fashion. Chief among these are PDGF[98], bFGF[115], insulin-like growth factor (IGF)[116] and thrombospondin[100].

Inflammatory cells

The presence of macrophages, neutrophils and lymphocytes in the vein graft wall has led to the suggestion that they may influence vessel wall healing and hence IH[117]. The demonstration of a monocyte-derived growth factor similar to PDGF[118] and the mitogenic action of interleukin (IL) 1 for SMCs supports this view[119]. The relative importance of these mitogens is unclear, however, and the results of immunosuppressive regimens to reduce IH have been variable[120,121]. The absence of functional lymphocytes in athymic nude rats has little influence on the development of IH following angioplasty[122].

Growth factors

Present understanding of the relative importance and specific roles of the growth factors that influence SMC behaviour is incomplete. There appears to be considerable redundancy and duplication in the system, the significance of which is unclear.

Platelet-derived growth factor. PDGF is released by platelets and can be produced by the endothelium[99] and SMCs[98]. It is composed of two polypeptide chains, A and B, the latter being encoded by the c-*sis* proto-oncogene[123]. The growth factor can therefore exist in three different isoforms: AA, AB and BB. The AB and BB isoforms are released by platelets and, as mentioned earlier, have a principally migratory effect on SMCs[124]. After injury, the SMC produces the AA isoform, which acts in an autocrine fashion to stimulate its own proliferation[113]. Administration of an antibody to PDGF in nude rats after carotid artery angioplasty results in a 41 per cent reduction in neointima formation[125]. PDGF is a competence factor enabling cells to move from the G0 to G1 phase of the cell cycle[123]. SMCs require a further 'progression factor' for DNA synthesis to take place; there is evidence that IGF and thrombospondin may perform this role. PDGF induces mRNA expression for both these compounds in vascular SMCs[116,126] and monoclonal antibodies to them inhibit SMC growth[101,127]. IGF is a polypeptide, also known as somatomedin C, and thrombospondin is a glycoprotein component of the extracellular matrix. A further illustration of the interaction between growth factors is provided by the observation that PDGF may also act (at least in part) via bFGF, which SMCs produce in response to PDGF[128]. Additionally, the mitogenic action of IL-1 has been shown to be due to the induction of the SMC PDGF-A gene[129].

Basic fibroblast growth factor. After the observation that the degree of direct SMC injury dictates the extent of subsequent IH, Lindner *et al.*[115] proposed that bFGF released by dying SMCs was able to stimulate surrounding surviving cells to migrate and proliferate. Infusion of bFGF into rats caused increased intimal SMC proliferation in injured carotid arteries; undisturbed vessels were unaffected. An antibody to bFGF was then used to reduce SMC proliferation after angioplasty in the rat carotid artery[130]. In addition, bFGF is a potent stimulator of endothelial regrowth[131].

Transforming growth factor (TGF) β. This is a polypeptide produced by platelets, the endothelium and SMCs at the site of injury, and is the most important factor promoting extracellular matrix production[123]. SMCs exposed to TGF-β synthesize proteoglycans, a major component of the early IH lesion[132]. TGF-β may also have some role in SMC proliferation through an interaction with other growth factors. At low concentrations, TGF-β promotes both SMC proliferation and migration via an interaction with PDGF, while having an inhibitory action at higher concentrations[133,134]. When cultured SMCs were exposed to a mixture of growth factors, the net effect of TGF-β on DNA synthesis was largely inhibitory, except at low concentrations[135].

Based on the above, it can be hypothesized that an early burst of SMC proliferative and migratory activity after injury may be caused by PDGF from platelets, the endothelium and SMCs, facilitated by a low initial concentration of TGF-β. Inflammatory cells may influence these early events via IL-1 induction of PDGF. The full response to PDGF would require the action of IGF and thrombospondin produced by proliferating SMCs. The bFGF released from dying SMCs or injured endothelium might provide an additional stimulus to these early events. At a later stage, higher concentrations of TGF-β would reduce PDGF-mediated proliferation and favour extracellular matrix secretion.

How do these theories of the aetiology of IH in response to injury fit in with knowledge of vein graft stenosis? First, there is a need to propose a relatively localized form of injury to explain the localized nature of most stenoses: possibly a clamp or valvulotome injury at the site of valves and tributaries[136]. Attractive though this explanation is, it appears to be erroneous. In a recent prospective study, Moody and colleagues[29] found no association between the sites of valves, tributaries, clamps and venotomies and the sites of subsequent stenosis. A second problem is the similar incidence of stenosis in reversed and *in situ* grafts: very different techniques must surely produce very different patterns of injury. Finally, there is uncertainty in experimental models about the significance of injury as the sole cause of graft stenosis. In animals, two studies demonstrated an increase in wall thickness (intimal plus medial) in injured veins[114,137], but this has not been confirmed in two others, in which no difference in wall thickness was found between distended[138] or stripped[139] veins and paired controls implanted using an optimal technique. Despite the abundant experimental evidence that injury can lead to IH, additional factors appear to be involved in the development of vein graft stenosis.

Haemodynamic factors

There is now considerable experimental evidence that IH in vein grafts is influenced by haemodynamic factors. In a detailed study, Dobrin and colleagues[140] demonstrated an inverse correlation between graft flow and intimal thickness in canine vein grafts. During laminar flow in blood vessels, the interaction between the blood and vessel wall occurs in the outermost layer known as the boundary layer. The force existing between t boundary layer and the wall is known as the shear stres Experiments have shown that it is low shear stress, and i particular a low variation in shear stress, associated with lo flow that is responsible for IH[141,142]. The endothelium pla a central role in the detection of these shear stresses and the transformation into vessel wall responses[143–145]. At the oth extreme, high shear stress can injure the endothelium[146] whic theoretically, might promote IH through some of t mechanisms discussed above. Increased wall tension due t exposure to arterial pressures has also been suggested as factor governing vein graft wall thickening, but this resul largely from medial thickening and not IH[140].

At vein graft anastomoses, two different patterns of intim thickening have been reported[147]. At the suture line, a healin response occurs that can lead to IH as a result of the complian mismatch between the vessels, producing a continuous deformation stress. This is less of a problem in vein grafts than i prosthetic conduits, where the mismatch is far greater[148]. end-to-side anastomosis, IH also develops at the heel and t of the graft and in the floor of the recipient artery. These coinci with the sites of boundary layer separation caused by turbule flow[148,149]. A wide inlet angle > 15° and reduced distal outflo promote this turbulent flow and exacerbate IH.

Such haemodynamic factors provide a good explanation f anastomotic but not for intragraft stenosis. For a foc intragraft lesion one must propose a localized abnormality flow within the graft, possibly at the site of valves or tributarie producing boundary layer separation. As already indicate there is little evidence to support such a proposal. Howeve the background level of IH in the graft on which a stenos develops may be determined by these haemodynamic factor

Other factors

Theoretically, lipids may play a role in the development stenosis although this remains to be proven. Vein graft accumulate lipid in their wall[150] and lipids can alter endotheli permeability and function[151]. However, in a primate vein gra model hypercholesterolaemia was not associated with increase IH[152]. Raised lipoprotein fraction levels have been associate with stenosis occurring 5 years after coronary artery vein bypa grafting[153], but at this time such stenosis is likely to b atherosclerotic in nature and atherosclerosis is already know to be associated with raised lipid concentrations. As yet n association between raised lipid levels and lower-limb gra stenosis has been described. Vein wall ischaemia has bee suggested as an important stimulus for IH. In a rat vein gra model the degree of IH was inversely related to the number capillaries in the wall of the graft[69]. Vessel wall ischaemia i most severe in the outer media, which relies on the vas vasorum, and SMC necrosis is seen here. As discusse previously, this may lead to the release of bFGF, a potent SM mitogen.

A multifactorial hypothesis

The aetiology of vein graft stenosis requires further study, a present knowledge is incomplete. It appears, however, that th aetiology is multifactorial. For anastomotic stenosis there i convincing evidence that haemodynamic factors, includin deformation stress and turbulent flow, promote IH. In the cas of intragraft stenosis, pre-existing venous intimal thickenin may be an important contributor to subsequent IH[77] and although the valves can produce stenosis, this is not as freque as was once thought[29]. Injury to the vein leads to a healin response involving platelets, the endothelium, SMCs, inflammatory cells and a range of growth factors. Wall ischaemia an SMC necrosis may provide additional mitogens. In the arteria environment, the endothelium may fail to achieve a full confluent layer, lipids may accumulate in the graft and th endothelium may function abnormally. Pulsatile shear stresse also act via the endothelium to regulate wall thickness. Thes and other unknown factors may lead to areas in which th ble 2 *Summary of pharmacological agents used for the prevention of intimal hyperplasia*

ug	Animal model	Clinical trial
tiplatelet agents (ASA, dipyridamole, loprost, daltroban)	Rabbit artery IH reduced[162] Rat artery IH unchanged[165] Primate and canine vein graft IH unchanged[166,167]	No reduction in coronary restenosis rate[163,164] CABG patency rate improved[16] Infrainguinal vein graft patency rate unchanged[95]
lcium antagonists	Small reduction in rabbit vein graft IH[169]	No reduction in coronary restenosis rate[170,171]
vastatin	Rabbit artery IH reduced[172]	Mixed effect on coronary restenosis rate[173,174]
sh oil	Canine vein graft IH reduced[175]	Mixed effect on coronary restenosis rate[176,177]
parin	Rat artery IH reduced[178,179] Rabbit artery IH reduced[181] Mixed effect on rabbit vein graft[182–184]	Coronary restenosis rate unchanged (short course)[180] Long-term (3–6 months) LMWH results awaited
E inhibitors	Rat artery IH reduced[185,186] Baboon and pig artery IH unchanged[188,189] Rabbit vein graft IH reduced[190]	No reduction in coronary restenosis rate[187]
closporin	Reduced medial thickening in rat artery[191]	
azosin	Rabbit artery IH reduced[192] Rat vein graft IH unchanged[193]	
eroid	Rabbit artery IH reduced[121] Canine vein graft IH unchanged[120]	

A, acetylsalicylic acid; CABG, coronary artery bypass graft; ACE, angiotensin-converting enzyme; IH, intimal hyperplasia; LMWH, low molecular ight heparin

aling response in the vein wall is abnormally excessive, sulting in stenosis.

reatment and prevention

urrent management of vein graft stenosis is based largely on rly detection and intervention before graft failure. A selective licy is usually adopted because some stenoses remain stable ithout progression to graft occlusion[154]. The consensus view that haemodynamically significant (fall in ankle:brachial terial pressure index >0·2), symptomatic and severe >70 per cent) stenoses, together with those showing evidence progression on serial surveillance scans, warrant interntion[32,41]. The benefit of this policy in terms of subsequent aft patency rates has not been studied in a randomized trial, ut there is retrospective evidence that it does lead to a gnificant improvement[27,155]. The majority of short stenotic sions can be adequately treated by percutaneous angioasty[37,38], although for longer stenoses (>2 cm) or multiple sions more durable results are obtained with an interposition r jump graft[33,40]. To adopt strategies to prevent graft stenosis, formation on their aetiology is needed. Prevention is currently ased on minimizing vein graft injury at the time of surgery. xperience with pharmacological agents for the prevention of H has been disappointing, although several agents may prove be of benefit in the future.

revention of injury

everal procedures used in the preparation of either *in situ* or eversed vein grafts have been identified as causing vein wall jury. Dissection alone producing spasm of the vein is sufficient o produce endothelial loss[156]. For reversed grafts, high-ressure (300 mmHg) distension of the vein and storage for rolonged periods should be avoided[157,158]. Distension with old saline solution rather than warm blood is particularly armful[159]. For *in situ* grafts, the valvulotome is the main cause f vein wall injury[35,36]. Although the use of angioscopy to erform controlled valvulotomy under direct vision enables this jury to be minimized[160,161], whether this reduces the ncidence of subsequent stenosis will be determined only by andomized comparative studies.

Pharmacological agents

Numerous drugs have been shown to influence the development of IH and several have now been evaluated in human studies. Unfortunately, no clear benefit has to date been demonstrated for any of these agents. *Table 2* outlines the conflicting results obtained in various animal models and the results of clinical studies, the majority of which have been concerned with the prevention of restenosis after coronary angioplasty. The initial lack of success in these studies is disappointing but there remain several possible avenues for future research. A combination of agents (heparin plus angiotensin-converting enzyme inhibitor) has been shown to have an additive effect and requires further exploration[194,195]. Non-anticoagulant fractions of heparin that retain their antiproliferative action may be potentially useful, as the dose of unfractionated heparin is currently limited by the bleeding complications it produces. Growth factor antagonists are being evaluated and initial results in animals are encouraging[196]. Topical treatment of the vein at surgery is another possibility recently reported by Simons and colleagues[197]. They have shown that the proto-oncogene c-*myb* can be inhibited *in vivo* by a gel containing antisense oligonucleotides applied to the wall of the exposed vessel; this led to a dramatic reduction in IH. Finally, it has recently become possible to introduce recombinant DNA into endothelial cells and induce them to produce large quantities of antithrombotic agents such as tissue plasminogen activator[198]. Such gene therapy has great therapeutic potential, since the modulated endothelial cells may be seeded on to sites of injury and graft surfaces, providing an ideal drug delivery system.

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Review

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Biliary drainage in obstructive jaundice: experimental and clinica aspects

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Jaundiced patients undergoing invasive diagnostic and therapeu procedures are at increased risk of complications and death. Desp the large number of clinical and experimental investigations carried o to identify relevant risk factors, no single parameter has been found be consistently useful in predicting morbidity or mortality. Bilia decompression was initially employed by surgeons and subsequently interventional radiologists. More recently, endoscopic retrogra cholangiopancreatography has provided an alternative route decompression of the biliary tree and preliminary data using this meth are encouraging. Although there are enthusiastic proponents of vario therapeutic techniques, controlled trials have not been convincing highlighting the benefits of biliary drainage or in determining the be approach. This article reviews the literature pertaining to this compl surgical problem; an attempt has been made to balance the advantag and disadvantages of biliary decompression as palliation and/ preliminary treatment for extrahepatic biliary obstruction.

Obstructive jaundice is often a clinical manifestation of disease of the extrahepatic biliary system or pancreas. Surgical procedures in jaundiced patients are associated with significant rates of morbidity and mortality, due mainly to the development of postoperative complications such as sepsis, bleeding disorders and renal failure[1–5]. Therapeutic endoscopic and radiological procedures are associated with similar problems although the frequency is less well documented[6–8]. Experimental and clinical studies have identified several aetiological factors including hypotension, impaired nutritional status, depressed immune function, hepatic dysfunction and the presence of toxic substances (bilirubin, bile salts, endotoxin) in the circulation[4,5,9].

Several risk factors associated with surgery in obstructive jaundice have been identified. A high serum bilirubin concentration in jaundiced patients undergoing pancreatic resection is recognized as a predictor of mortality and is associated with an increased frequency of renal insufficiency, septic complications and postoperative haemorrhage[10]. Hunt[11], in 1980, reported that a high serum bilirubin level (>300 μmol/l), low glomerular filtration rate (<50 ml/min), the presence of fibrinogen degradation products and endotoxaemia were associated with an increased mortality rate. In 1981, Pitt *et al.*[4] analysed 15 clinical and laboratory parameters in 155 consecutive jaundiced patients undergoing bile duct surgery in an attempt to define a subpopulation at greatest risk. They found eight factors that correlated with morbidity and mortality (malignancy, age >60 years, haematocrit <30 per cent, white cell count $>10^{11}$/l, and levels of albumin <30 g/dl, bilirubin >170 μmol/l, alkaline phosphatase >100 units/l and creatinine >115 μmol/l). In a retrospective study of 373 patients undergoing surgery for relief of biliary obstruction, Dixon *et al.*[12], using multivariate analysis, demonstrated only three factors that correlated with morbidity and mortality (haematocrit <30 per cent, bilirubin level >200 μmol/l and malignancy). Su *et al.*[13] studied 770 consecutive patients undergoing biliary surgery over a 3-year period and analysed 36 clinical and biochemical parameters to define those at greatest risk. Twelve factors were significantly correlated with hospital mortality, and multivariate analysis revealed that septic shock, malignant obstruction, a seru albumin level <30 g/l, a history of hypertension and a plasn urea nitrogen concentration >20 mg/dl had an independe significance in predicting postoperative death. The presence more than two of these risk factors identified a group of patie with an 18 per cent mortality rate[13]. In a prospective study patients with benign biliary obstruction, only serum bilirut concentration correlated with mortality[1] whereas, in retrospective study of a similar group of patients, three facto (creatinine, albumin and bilirubin levels) correlated wi mortality[2]. In all these studies the serum bilirubin lev reflecting the severity of jaundice, seemed to be a significa factor determining outcome. These observations lead to tl theory that relief of obstructive jaundice (by surgic radiological or endoscopic drainage techniques) to lower seru bilirubin concentration causes improvement in renal, liv synthetic and haematological abnormalities with consequent improved morbidity and mortality rates.

The focus of the present review is the role of biliary draina in the management of obstructive jaundice. The path physiological effects of obstructive jaundice and th consequences are described, followed by a description relevant animal models. The results of animal studies a discussed and summarized. The development of biliary draina in patients is reviewed, followed by a general evaluation of t indications for and results of each technique.

Pathological effects of obstructive jaundice

Since Wardle and Wright[14] demonstrated an associati between systemic endotoxaemia and renal failure in obstructi jaundice, endotoxin has been increasingly implicated in t pathophysiology of complications seen in jaundiced patients[1] It is postulated that in obstructive jaundice there are two maj contributing factors in the development of endotoxaemia. Firs the absence of bile salts in the gastrointestinal tract means loss of their antiendotoxin effect, resulting in a large pool endotoxin in the large bowel that can be absorbed into th portal circulation[16–19]. Second, impairment of hepatic Kupff

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ll phagocytic function in obstructive jaundice allows spillover gut-derived endotoxin into the systemic circulation. Systemic idotoxaemia may then activate the inflammatory response, ading ultimately to impairment of organ function. Other ctors such as reduced production of antiendotoxin secretory nmunoglobulin A from the liver[20], depression of the ononuclear phagocytic system[21–28], deficient cell-mediated id humoral immunity[29–33], and changes in mucosal rmeability and blood flow[34] may occur, and are detrimental the host. The clinical manifestations of these effects include increased incidence of sepsis, haemorrhagic complications, nal failure and multiple organ failure[1,35,36]. Other possible fects include impaired wound healing and an increased icidence of wound dehiscence[37,38].

xperimental aspects of biliary drainage

he study of some of the pathophysiological phenomena in bstructive jaundice has been carried out with a variety of nimal models. The simplest of these uses bile duct ligation, ut other models for studying the effects of relief of obstruction y both internal drainage (bile returned to the gastrointestinal act) and external drainage (bile diverted away from the astrointestinal tract) have been developed.

ile duct ligation

he rat bile duct ligation model is well established for the study f many aspects of obstructive jaundice, including endo- xaemia, renal function, wound healing and immunological nction[17,22,39,40]. The operative procedure is more correctly escribed as bile duct ligation and division, because the bile uct is doubly ligated and then divided between the ligatures reduce the possibility of spontaneous recanalization[41]. Other nimal models for biliary obstruction are available. Bile duct gation in dogs has been used to investigate the effect of biliary bstruction on hepatic reticuloendothelial function[23], and abbits have been used to study changes in reticuloendothelial nd lymphocytic immune function following biliary obstruction nd relief of obstruction by internal drainage, via a cholecysto- junostomy[24]. Larger animals have a gallbladder (unlike the at) and a reversal procedure such as cholecystojejunostomy technically easy to perform; there is no convenient model for xternal biliary drainage in these species.

Mice have been used to study bacterial translocation in bstructive jaundice[42]. Unfortunately, with this model, simple echniques for internal and external biliary drainage are not vailable. The rat is therefore the most widely used experimental nimal for studies of obstructive jaundice as large numbers can e used, rats are relatively inexpensive, and both internal and xternal drainage procedures have been described for them. owever, rats are highly resistant to the pathophysiological ffects of endotoxaemia. Zwiefach[43] in 1961 reported the ollowing relative lethal dose$_{75}$ for circulatory collapse ollowing endotoxin challenge in various animals: cat, 1; rabbit, ·5; dog, 8; guinea-pig, 20; and rat, 300. To overcome this high esistance, and so allow widespread use of the rat to study the evelopment and effects of endotoxaemia, a technique involving he administration of lead acetate was developed to produce ensitivity to endotoxin[44].

nternal drainage: choledochoduodenostomy

This rat model was first described by Ryan *et al.*[45] in 1977 and s used to study reversal of biliary obstruction by internal drainage and return of bile to the gastrointestinal tract. The operation involves a laparotomy at a given time after bile duct igation (for example, 2 or 3 weeks) and anastomosis of the dilated proximal common bile duct (CBD) to the duodenum. The anastomosis is splinted by a Teflon (Du Pont, Stevenage, UK) tube. Although the procedure has been reported to be well tolerated with negligible mortality[45], it has several disadvantages. The reversal operation is carried out on a dilated thin-walled friable bile duct, making insertion of a purse-string suture difficult, and biliary leakage may occur. The bile duct may also require mobilization, causing significant bleeding or inadvertent puncture of the biliary system. Diamond *et al.*[46] overcame these problems by modifying the procedure. At the initial bile duct ligation a Silastic (Dow Corning, Reading, UK) cannula is introduced into the choledochus and held in place with silk ties passed around the duct. The lower end of the cannula is then kinked and ligated to cause biliary obstruction. The reversal operation is then simply a matter of dividing the ligature and introducing the cannula into the duodenum through a purse-string suture.

External drainage: biliary fistula

This rat model involves cannulation of the CBD and exteriorization of the cannula via a subcutaneous tunnel. The cannula may be connected to the cage via a swivel joint so that free movement of the rat is possible, and bile may be drained and collected continuously[47]. The model mimics percutaneous external biliary drainage in humans, in which biliary obstruction is relieved but bile is not returned to the gastrointestinal tract. It has been used to study the effect of absence of gastrointestinal bile flow on the development of endotoxaemia[16] and to compare reversal of endotoxaemia by internal and external biliary drainage[48,49]. This rat biliary fistula model has several disadvantages, including dislodgement of the cannula, biliary leakage, twisting and kinking of the cannula, and chewing of the cannula by the animal. A more serious problem is infection of the cannula and biliary system from an external source.

External drainage: choledochovesical fistula

In 1977, Burke *et al.*[50] described a choledochovesical fistula; the CBD was anastomosed to the urinary bladder via a Silastic cannula. This was modified by Diamond and Rowlands[51] in 1990. At the initial procedure a Silastic cannula is inserted into the bile duct and held in place with silk ligatures. The lower end is introduced into the urinary bladder through a purse-string suture. The middle portion of the cannula is then kinked and ligated to produce biliary obstruction. At the reversal operation the ligature is divided, thus allowing bile flow from the biliary tree to the urinary bladder and hence to the exterior. When cannulas were cultured no bacteria were grown, suggesting that this is a sterile model for external biliary drainage[46]. Relief of biliary obstruction is usually followed by a postcholestatic choleresis[52]. External drainage causes bile to be lost to the exterior and fluid must be replaced by daily subcutaneous injection of saline for the first 4–5 days after the reversal procedure[49].

Other drainage models

To study the effects of the absence of bile from the small intestine without prior biliary obstruction, Bergesen *et al.*[53] developed a choledochocolic fistula. Ascending cholangitis may occur with this model and the choledochovesical fistula is probably better for studying the absence of bile without intercurrent infection[54]. The direct toxic effects of bile salts in the systemic circulation were studied by Byers *et al.*[55] in 1952; a choledochocaval shunt was made by anastomosing the CBD to the inferior vena cava, so producing hyperbilirubinaemia without biliary obstruction. This is a technically difficult procedure with a high mortality rate; it is used infrequently.

Animal experimentation results

Many aspects of obstructive jaundice have been studied using these models, but caution is advised in the interpretation of results and their clinical extrapolation. Using the bile duct ligation model it has been shown that in biliary obstruction there is depressed wound healing[37], portal hypertension and structural liver damage[56,57], significant portal and systemic endotoxaemia[17,48,58], decreased bacterial trapping[25], increased sensitivity to septic challenge[59], decreased reticuloendothelial cell function[60,61], reduced T cell responses[30], depressed non-specific cell-mediated immunity[31], decreased bacterial clearance[23] and increased bacterial translocation[42]. Greve *et al.*[62] demonstrated that T cell function was depressed in bile duct ligated rats with normal gut flora, but not in bile duct ligated germ-free animals. This implies that endotoxin released in rats with normal bacterial flora produces the immune suppression.

These results suggest that in obstructive jaundice there is not only impairment of hepatocellular function but also depression of hepatic Kupffer cell activity and ultimately hepatic structural damage, leading to the development of portal hypertension. In addition, systemic effects such as depression of phagocytosis and cellular immunity, impairment of wound healing and the development of bacterial translocation occur.

Results following the reversal of biliary obstruction have been conflicting. Gouma *et al.*[48] showed that, following relief of biliary obstruction in rats by internal drainage, endotoxaemia was reduced, but that after external drainage endotoxaemia was unaffected. In addition, using a septic challenge model (caecal ligation and puncture), they showed that the mortality rate in jaundiced rats was reduced following internal but not external drainage[49]. It was concluded that these differences between internal and external drainage were due to the return of bile to the gut in the former. On the other hand, using choledochoduodenostomy and choledochovesical fistula models, Diamond and Rowlands[51] showed that internal and external drainage were equally effective in reversing endotoxaemia. The mortality rate following septic challenge was similar in both groups, which may be due to the sterile nature of the choledochovesical fistula as a form of biliary drainage. T cell suppression in obstructive jaundice is reversed by biliary decompression[30]; Thompson *et al.*[63] showed that T cell dysfunction returns more quickly to normal with internal than external biliary drainage. Other authors have found that mononuclear phagocytic capacity is restored after a short period of internal biliary drainage[33,64].

Clinical aspects of biliary drainage

Biliary drainage before definitive surgery

Decompression of the biliary tract to reduce the serum bilirubin level before definitive surgery for carcinoma of the ampulla of Vater was first recommended by Whipple *et al.*[65] in 1935. A two-stage procedure was used, consisting of surgical drainage of the biliary tract (cholecystogastrostomy) followed 3–4 weeks later by resection of the tumour. Although the effect of biliary decompression was favourable, intra-abdominal adhesions made the second operation more complex and the mortality rate was not significantly improved. The introduction of the Chiba needle for percutaneous liver puncture, and of ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP), provided new diagnostic and therapeutic options. External biliary drainage was used to provide decompression of the biliary tract as a first stage in the preparation of jaundiced patients for operation[66]. It was postulated that this would improve liver function and reduce toxic effects and complications when a definitive operation was carried out 2–3 weeks later[67].

Several early reports showed improvement in operative morbidity and mortality rates after external preoperative biliary drainage[66–69] (*Table 1*). These studies were retrospective, non-randomized and used historical controls for comparison. Three additional reports with concurrent but non-randomized controls also favoured preoperative biliary drainage. Denning *et al.*[72] reported a lower operative mortality rate (16 per cent) in 25 patients undergoing preoperative drainage than in 32 jaundiced controls (25 per cent). Although this was not statistically significant, there was a significantly higher morbidity rate in the former group (28 *versus* 56 per cent). Norlander *et al.*[75] reported a 14 per cent mortality rate in patients who had undergone preoperative drainage compared with 21 per cent in controls. In 1984, Gundry *et al.*[78] report a 4 per cent postoperative mortality rate and an 8 per ce morbidity rate in patients undergoing preoperative draina compared with 20 and 52 per cent respectively in those receivi surgery without such drainage. At this time there were ma proponents of preoperative drainage and a collective review the literature revealed that percutaneous external drainage w performed in most reported series and in 70 per cent of a reported patients[87,88].

Nevertheless, there were obvious weaknesses in these ear studies and there appeared to be a high incidence procedure-related complications such as bleeding, bile leakag sepsis and catheter dislodgement. The initial enthusiasm for th technique was tempered by the conclusive demonstratio through several prospective randomized controlled clinic trials, that preoperative external biliary drainage does n improve operative morbidity and mortality rates in jaundice patients[73,79,81,85]. Hatfield *et al.*[73] and McPherson an colleagues[79] highlighted the significant incidence of loc complications such as cannula sepsis, bleeding and bilia leakage associated with external drainage, and Pitt *et al.* stressed the significant increase in hospital cost. The reservations about local complications have been emphasize by others[86]. In addition, although hyperbilirubinaemia retur rapidly towards normal, preoperative biliary drainage has litt impact on impaired renal, haematological and immunologic function, and hepatic synthetic function takes several weeks t recover fully[75]. The incidence of procedure-related compl cations is extremely important and in many series this was n included in the overall morbidity rates. Mueller *et al.*[89], in 198 analysed 200 consecutive percutaneous biliary drainages an concentrated on complications inherent to the procedur Despite achieving successful drainage in 94 per cent patients, severe periprocedural complications occurred i 8 per cent of cases (death, three; septicaemia, sever haemorrhage, six). It was apparent that the benefits percutaneous transhepatic drainage were accrued at the expens of significant morbidity[76,86].

Bile leakage, haemorrhage and cholangitis constitute th majority of procedure-related problems; pneumothorax i described in 0·8 per cent of cases[66] and intra-abdomina bleeding occurs in a similar proportion. Haemobilia i observed[6,90] in 3·6 per cent of cases. Biliary leaks are seriou and reported[91] in 2 per cent of patients. Infection is the majo hazard and the incidence increases proportionately with th duration of drainage[79]. Despite the development of a close drainage system by Blenkharn *et al.*[92] in 1984, sepsis remain a major consideration when preoperative biliary drainage i used[93]. In a review of all reports on preoperative externa drainage from 1974 to 1984, Gouma and Moody[77] conclude that the hazards of the technique outweighed any possibl advantages. External biliary decompression before surgery has therefore, been abandoned by most surgeons.

The failure of external percutaneous drainage to improv outcome led to an interest in the efficacy of preoperative interna drainage, but clinical experience with this technique is limited Theoretically, internal drainage may produce better results b preventing external loss of fluid and electrolytes, and b avoidance of the disruption of the enterohepatic bile sal circulation. Smith *et al.*[80] demonstrated improved rena function and fewer surgical complications in patients who had a percutaneous stent to allow internal biliary drainag compared with a control group who underwent immediate surgery. However, this benefit was lost when the morbidity associated with percutaneous stent insertion was taken int consideration. Internal drainage using percutaneous stent placement is still associated with the complications accompanying liver puncture.

Endoscopic stent placement allows internal drainage without such complications; in a randomized comparison of endoscopic *versus* percutaneous stent insertion, Speer and colleagues[94] demonstrated a higher success rate for relief of ble 1 *Summary of results in published series of preoperative biliary drainage*

eference	Year	Drainage	Controlled randomized prospective study	Morbidity rate (%)*	Mortality rate (%)*	Technique beneficial	Comments
akada *et al.*[68]	1976	External	No	—	4 *versus* 41	Yes	Small series (28 patients)
akayama *et al.*[66]	1978	Internal and external	No	—	8·2 *versus* 28·3	Yes	Historical controls used in comparison
ooley *et al.*[70]	1979	Internal and external	No	5	24	—	
lderson *et al.*[71]	1981	Endoscopic	No	20	0	Yes	Small study size (five patients)
enning *et al.*[72]	1981	Internal and external	No	28 *versus* 56	16 *versus* 25	Yes	Preoperative drainage period allowed time for better patient preparation before surgery
atfield *et al.*[73]	1982	External	Yes	14 *versus* 15	14 *versus* 15	No	First controlled randomized prospective trial
cPherson *et al.*[74]	1982	Internal and external	No	—	24	No	High incidence of sepsis with external drainage
orlander *et al.*[75]	1982	Internal and external	No	—	14 *versus* 21	No	Emphasized importance of patient selection
tambuk *et al.*[76]	1983	External	No	9	5	Yes	Risk of percutaneous transhepatic drainage outweighed benefit in deeply jaundiced patients with advanced malignancy
obien *et al.*[69]	1984	External	No	15 *versus* 44	12 *versus* 30	Yes	
ouma and Moody[77]	1984	Internal and external	No	18 *versus* 18	9 *versus* 9	No	
undry *et al.*[78]	1984	Internal and external	Yes	8 *versus* 52	4 *versus* 20	Yes	
cPherson *et al.*[79]	1984	Internal and external	Yes	33 *versus* 42	32 *versus* 19	No	Benefits of preoperative drainage negated by inherent procedure-related complications
mith *et al.*[80]	1984	Internal	Yes	14 *versus* 75	7 *versus* 20	No	Concluded that morbidity rates associated with percutaneous transhepatic drainage would preclude its widespread use
itt *et al.*[81]	1985	Internal and external	Yes	46 *versus* 53	8 *versus* 5	No	Emphasized increased hospital cost of procedure
ygidakis *et al.*[82]	1987	Endoscopic	Yes	—	0 *versus* 10	Yes	Recommended preoperative endoscopic drainage
ypins *et al.*[83]	1987	Internal and external	No	—	—	No	
rede and Schwall[84]	1988	Internal	No	17 *versus* 31	1 *versus* 6	Yes	Recommended preoperative endoscopic drainage
irenek and Levine[85]	1989	Internal and external	No	37 *versus* 32	11 *versus* 11	No	High incidence (18%) of procedure-related complications
hen[86]	1991	External	Yes	—	—	No	

Where known, values for drained *versus* not drained before operation are given

aundice and a lower 30-day mortality rate for the endoscopic method. The higher mortality rate after percutaneous drainage rose from complications associated with liver puncture. In a andomized trial of patients undergoing surgical resection for arcinoma of the head of the pancreas, endoscopic internal iliary drainage significantly reduced the incidence of biliary nfection, bacteraemia and intraoperative bleeding[82]. Trede and chwall[84] reported that preoperative endoscopic internal rainage decreased the incidence of postoperative complications n patients with pancreatic carcinoma. There are, however, only small number of reports on the use of endoscopic internal rainage as a preparatory procedure in obstructive jaundice nd a definitive decision on its efficacy requires further ontrolled trials.

Biliary drainage for palliation of obstructive jaundice

Obstruction of the extrahepatic bile duct system by incurable malignancy challenges the surgeon to achieve satisfactory relief of jaundice and maximal life expectancy, while incurring minimal risk to the patient[88]. Pancreatic cancer represents 10 per cent of all gastrointestinal neoplasms and has seen a remarkable threefold increase in incidence[95,96]. Despite an improvement in resectability rates[97], still only 8–15 per cent of patients are suitable for curative surgery. For the majority, therefore, a palliative procedure is required. Operative bypass procedures are associated with a mortality rate[98] as high as 25 per cent and so non-operative palliation seems an attractive alternative to surgery. Various authors have addressed the questions of whether non-operative management is a better option and by which route drainage should be performed, percutaneous or endoscopic.

Comparison of various techniques requires the evaluation of technical success rate, therapeutic failure rate, 30-day mortality rate, complication rate, occlusion rate, hospital stay and mean survival[99–125] (*Table 2*). Gazzaniga *et al.*[115] reported excellent results of a 12-year experience of percutaneous stent insertion in 362 patients with biliary obstruction. Technical success was obtained in 350 patients

Table 2 *Summary of results in published series of endoscopic, percutaneous and surgical palliation of malignant biliary obstruction*

Reference	Year	No. of patients with malignancy	Technical success rate (%)	Successful drainage rate (%)	30-day mortality rate (%)	Early morbidity rate (%)	Media surviv (days)
Percutaneous transhepatic drainage							
Pereiras *et al.*[100]	1978	12	100	83	—	58	—
Hoevels and Ihse[6]	1979	13	—	57	29	38	—
Pollock *et al.*[101]	1979	26	91	73	—	27	—
Burcharth *et al.*[102]	1981	94	82	66	30	15	62
Mueller *et al.*[89]	1982	109	92	—	10	17	—
Coons and Carey[103]	1983	62	—	60	27	13	—
Leung *et al.*[104]	1983	48	88	—	17	—	190
Burcharth[105]	1984	455	88	73	—	6	98
Dooley *et al.*[106]	1984	40	86	70	25	29	92
Malangoni *et al.*[88]	1985	36	73	97	25	56	150†
Voegeli *et al.*[107]	1985	76	97	92	27	20	140†
Devereux and Greco[108]	1986	16	—	—	20	46	—
Bornman *et al.*[109]*	1986	25	84	62	8	28	133
Joseph *et al.*[110]	1986	39	90	—	49	53	47
Speer *et al.*[94]*	1987	36	76	61	33	61	113
Bear *et al.*[111]	1989	25	96	100	16	64	120
Schild *et al.*[112]	1989	220	—	82	1	22	—
Adam *et al.*[114]	1991	41	100	92·5	—	5	105
Gazzaniga *et al.*[115]	1991	362	97	82	—	15	—
Murai *et al.*[116]	1991	92	86	—	—	—	—
Endoscopy							
Leung *et al.*[104]	1983	64	89	—	16	—	154
Hagenmueller[117]	1984	454	84	—	8	26	47–81
Huibregste and Tytgat[118]	1984	297	89	86	15	17	162†
Siegel and Snady[99]	1986	277	89	70	18	21	129
Sonnenfeld *et al.*[119]*	1986	19	100	90	21	22	120
Kiil *et al.*[120]	1987	272	92	88	22	40	62
Speer *et al.*[94]*	1987	39	89	81	15	18	159
Lindstrom *et al.*[121]	1988	89	79	94	26	14	—
Andersen *et al.*[122]*	1989	33	100	97	15	30	81
Huibregste *et al.*[123]	1989	33	100	97	3	9	—
Polydorou *et al.*[124]	1991	190	89	82	29	22	100
Regula *et al.*[125]	1991	79	82	95	—	4	145
Surgery							
Malangoni *et al.*[88]	1985	70	—	—	17	36	420†
Devereux and Greco[108]	1986	17	100	100	0	6	—
Bornman *et al.*[109]*	1986	25	76	84	20	32	105
Sonnenfeld *et al.*[119]*	1986	22	100	86	14	36	120
Andersen *et al.*[122]*	1989	19	76	63	32	20	108
Bear *et al.*[111]	1989	13	100	86	14	30	135

*Prospective controlled randomized trial; †mean value

with a mortality rate of 0·8 per cent. The cumulative complication rate was 14·6 per cent: stent obstruction (1·9 per cent), dislodgement (4·1 per cent), haemobilia (4·1 per cent), haemoperitoneum (0·2 per cent), cholangitis (1·6 per cent) and choleperitoneum (2·7 per cent). Yee and Ho[126] were also firm proponents of the percutaneous route for palliative and temporary drainage. Malangoni and colleagues[87] concluded that percutaneous decompression of the biliary tree is a useful palliative treatment for patients with proximal biliary obstruction from malignancy when estimated operative risk is high, but that operative decompression offers more patients the opportunity for longer survival with less ultimate morbidity and mortality. Leung *et al.*[104] reported a retrospective experience of management of malignant obstructive jaundice at the Middlesex Hospital, London, in the 6 years to Decembe 1982; 180 patients were treated by resection, surgical bypass percutaneous prosthesis insertion, endoscopic prosthesi insertion or endoscopic sphincterotomy. Few conclusions coul be drawn, but all the methods provided reasonable short-terr palliation, and prosthetic techniques seemed to have legitimate role in the frail and elderly. Siegel and Snady[99] wer enthusiastic about the merits of endoscopic palliation and, i a retrospective analysis of 277 patients, concluded tha endoscopic biliary drainage had a low procedure-relate mortality rate, a low incidence of major complications an involved a shorter hospital stay. Although management of dista malignant biliary obstruction by endoscopic endoprosthesi insertion is well established[127], its place in the management o

oximal malignant biliary obstruction remains controversial.
a prospective study carried out at the Middlesex Hospital,
0 patients, of mean age 73 years, with proximal biliary
struction were treated by endoscopic endoprosthesis
sertion[124]. Patients were subdivided according to the Bismuth
assification[128] (type I, 58; type II, 54; type III, 78). A
mbined percutaneous–endoscopic approach was employed
en appropriate. The cumulative technical success rate for
itial endoprosthesis insertion was 89 per cent and the overall
ccessful drainage rate was 82 per cent (type I, 91 per cent;
pe II, 83 per cent; type III, 73 per cent). Early reported
mplication rates were: type I, 7 per cent; type II, 14 per cent;
d type III, 33 per cent. The 30-day mortality rate was
per cent but only 3 per cent were procedure related. Median
rvival times were 21, 12 and 10 weeks respectively in the three
pes. The authors concluded that endoscopic insertion of a
gle endoprosthesis provides good palliation of proximal
alignant biliary obstruction in 80 per cent of patients.

Controlled trials were performed by Bornman *et al.*[109] and
eer and associates[94] to elucidate the best mode of palliative
ainage. Bornman and colleagues found no difference in
edian survival time (19 *versus* 15 weeks), complication rate
8 *versus* 32 per cent) or duration of hospitalization between
rcutaneous transhepatic endoprosthesis insertion and bypass
rgery. Speer and co-workers compared endoscopic with
rcutaneous stent insertion in malignant obstructive jaundice
d showed that endoscopic insertion had a significantly higher
ccess rate for relief of jaundice (81 *versus* 61 per cent) and a
gnificantly lower 30-day mortality rate (15 *versus* 33 per cent).
nnenfeld *et al.*[119] reported a non-randomized comparison of
doscopic endoprosthesis *versus* surgical bypass in 41 patients,
ut were unable to demonstrate any difference in survival.
owever, hospital stay was shorter and the incidence of major
mplications lower in patients managed without operation.

Shepherd *et al.*[129] and Andersen and colleagues[122], in two
ntrolled randomized prospective studies, compared endo-
opic palliation with operative bypass and agreed that there
as no significant difference in survival between treatment
roups, although there was a favourable trend for endoscopic
enting in the former series. Shepherd's group found that
atients who underwent endoscopic drainage spent less time in
ospital, even when they required readmission for stent
placement; there were fewer and less serious procedure-
lated complications and failure did not mean obligatory
rgery or a permanent external biliary fistula. Andersen *et al.*
ported less favourably: they demonstrated a decreased
rvival time (81 *versus* 108 days) and a higher complication
te (30 *versus* 20 per cent) with endoscopic palliation, although
ese differences were not statistically significant. The finding
at survival time is not affected by the method of drainage is
irtually unanimous and probably reflects the poor general
hysical status of patients with malignant disease.

Most would agree that endoscopic palliation is safer than
ercutaneous transhepatic stenting. It is technically very
uccessful in relieving jaundice and associated with fewer
omplications than surgery[121,124,130–132]. Hospital stay is
enerally shorter and the incidental development of duodenal
bstruction rare. Some have drawn attention to the higher
ncidence of late complications, namely blockage and
holangitis[113], although with the advent of the self-expandable
etal Wallstents (Schneider, Bulach, Switzerland) complication
ates have been greatly reduced[114]. In the event of blockage,
tent replacement is a simple and safe procedure in experienced
ands and fewer problems have been demonstrated with larger
alibre stents[123,133]. Episodic cholangitis seems to relate to the
iting of the stent; more problems develop when the stent
rotrudes through the papilla, although some authors have
laimed that this position is more desirable in the event of
etrieval being necessary[134].

Biliary drainage for benign disease

Percutaneous and endoscopic approaches to benign disease of the bile duct each have their proponents. However, it is becoming apparent that percutaneous dilatation of CBD stricture, although still widely practised, is associated with a recurrence rate of 20–30 per cent and more procedure-related morbidity[135].

There are certain benign conditions for which non-operative drainage is valuable[136]. The most common indications are stone retrieval and dilatation of benign stricture. However, non-operative drainage in benign disease is limited by morbidity such as sepsis and stent obstruction, and so is rarely employed in the long term under these circumstances. The successful use of temporary drainage has been reported in patients with acute suppurative cholangitis[137], recurrent benign stricture[138], sclerosing cholangitis[139], choledochal cyst[140], chronic pancreatitis[141], choledocholithiasis[142] and oriental cholangitis (recurrent pyogenic cholangitis)[143]. Soomers *et al.*[144] demonstrated that endoscopic insertion of a biliary endoprosthesis is a safe and effective treatment for huge CBD stones in high-risk patients in whom endoscopic sphincterotomy and attempts to remove the calculi have been unsuccessful.

Postoperative CBD stricture usually presents soon after the initial operation, but in some patients presentation is delayed. In many cases, non-operative biliary drainage is useful for treating concomitant sepsis or fistula, but experience suggests that surgical repair is associated with fewer long-term problems and similar overall morbidity and cost[145].

Acute suppurative cholangitis is associated with considerable morbidity and mortality. Lai *et al.*[146] carried out a prospective study of 82 patients with severe acute cholangitis over a 43-month period. The aim was to assess the potential benefits of emergency endoscopic biliary drainage, as the initial procedure, over the standard open surgical approach. A range of clinical and biochemical parameters was used to measure successful treatment. The hospital mortality rate for patients treated endoscopically was substantially lower than for those managed surgically (10 *versus* 32 per cent). Furthermore, complications relating to biliary tract decompression and subsequent definitive therapy were less frequent in patients treated endoscopically (34 *versus* 66 per cent).

The natural history of primary sclerosing cholangitis is poorly defined and its management remains controversial. This is a progressive disease and conventional surgical options have little influence on outcome[147]. Previous biliary surgery adversely affects outcome following orthotopic liver transplantation, but an endoscopic approach as a temporary therapeutic strategy holds some promise as a preliminary to transplantation[148,149].

Endoscopic diagnostic and therapeutic procedures are not without complications and sepsis is the major factor in procedure-related morbidity and mortality. Motte *et al.*[150] analysed 34 consecutive patients who experienced septicaemia within 3 days of endoscopic biliary drainage in an effort to identify risk factors for such sepsis. They concluded that pure diagnostic ERCP should be avoided in patients with an obstructed biliary tree if drainage cannot be implemented simultaneously and added that drainage should be as complete as possible. Appropriate antibiotic therapy should be administered prophylactically with special attention to cover for coliforms and *Pseudomonas* species; the duration of prophylaxis should be governed by the quality of drainage.

Conclusions

Animal models of biliary obstruction and drainage have increased knowledge of the basic pathophysiology of obstructive jaundice and its complications. Several important features (biliary obstruction, lack of intraluminal bile salts, altered gastrointestinal structure and function) appear to be important in the development of endotoxaemia. When hepatic reticuloendothelial dysfunction allows endotoxin to spill over into the systemic circulation, pathological effects such as impairment of immune function may occur, leading to systemic complications. Relief of biliary obstruction, preferably into the gastrointestinal tract, may help to reverse some of these effects and produce improvement in the clinical condition.

Clinical studies on biliary decompression have demonstrated that external drainage has limited benefit as a preparatory procedure before definitive surgery because of the high incidence of local complications that negate any benefits resulting from drainage. External biliary drainage is equally limited as a palliative treatment for malignant disease.

Internal biliary drainage may be useful in both of the above capacities as it restores the *status quo* in the gastrointestinal tract with respect to bile flow, as well as overcoming biliary obstruction. More clinical and experimental studies are required to provide supporting evidence for the apparent physiological, anatomical and immunological benefits of this therapeutic strategy. Internal biliary drainage is a better treatment option in malignant obstructive jaundice, and both radiological and endoscopic routes have been used successfully, independently or as a combined procedure. Although it is now widely accepted that endoscopic methods are associated with lower procedure-related morbidity and mortality rates, the percutaneous approach still has a role (e.g. for proximal lesions inaccessible via the papilla). Selection of optimal management for the individual patient requires in-depth evaluation by a skilled team consisting of an endoscopist, interventional radiologist and surgeon. With regard to benign disease, there is virtually no place for long-term external biliary drainage except where internal drainage has failed. Short-term internal drainage is beneficial in certain benign conditions before definitive surgical treatment.

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This month's digest by Professor Christian Herfarth and Dr Thomas Lehnert of Der Chirurg *is of the first quarter of 1993. A reciprocal summary of the best in the* BJS *written by Professor John Farndon appears in the German journal.*

ndocrine surgery

Medullary carcinoma of the thyroid has a sensitive and specific umour marker (calcitonin) and this allows the detection of ymptomatic disease at a preclinical stage. Frilling and ssociates[1] from Düsseldorf report experience with screening ymptomatic relatives of patients with medullary carcinoma f the thyroid. Between 1 April 1986 and 31 December 1991, 0 patients underwent surgical treatment for medullary ırcinoma of the thyroid. Thirty patients exhibited the sporadic rm of the disease and 20 cancer of the familial type. Seventeen atients had multiple endocrine neoplasia (MEN) type IIA and vo were considered to have the MEN IIB syndrome. One atient had a combination of medullary carcinoma of the ıyroid, phaeochromocytoma and Hirschsprung's disease. 'alcitonin determinations in 58 asymptomatic relatives of 11 atients with MEN IIA revealed abnormalities in nine. All nine atients underwent total thyroidectomy. Histopathological xamination demonstrated medullary carcinoma of the thyroid ı eight patients and C cell hyperplasia in one. At a mean ıllow-up of 30 months, eight of these patients were clinically nd biochemically free from tumour.

Flow cytometric analysis of tumour DNA content has been sed to provide additional prognostic information for a large umber of tumours. Böttger *et al.*[2] from Mainz applied this ıethod to 16 patients with medullary carcinoma of the thyroid. he 5-year survival rate for patients with diploid or hypoiploid tumours was 100 per cent, compared with 48 per cent r those with triploid or hypertriploid carcinoma. Aneuploid umours were more frequently demonstrable in patients with mph node metastases and high preoperative or postoperative rum calcitonin levels. In this small number of patients no orrelation was observed between DNA content of the tumour nd sex, age, preoperative carcinoembryonic antigen level, umour size, vessel invasion, histological staining (amyloid or ilver) or the presence of distant metastases.

Phaeochromocytoma is another component of the MEN yndrome and may be detected at an early stage by screening symptomatic individuals. Sporadic phaeochromocytoma is nore difficult to detect, as is the extra-adrenal catecholamine-roducing tumour. Hiller and colleagues[3] from Hanover report xperience with this rare condition. Between 1981 and 1991, en patients (five men, five women) underwent surgical reatment for extra-adrenal paraganglioma. The mean age was 2 (range 29–67) years. Seven of the ten patients were ıypertensive. Other symptoms included nausea, sweating, alpitations, retrosternal pain and tachycardia. A preoperative iagnosis was established in only seven patients. Noradrenaline leterminations in plasma and urine had a higher sensitivity han those of dopamine or adrenaline. Tumours were successully localized by computed tomography or ultrasonography n nine patients. Four of six patients studied had a positive *m*-iodobenzylguanidine scan. Potentially curative surgery was ossible in nine of ten patients although three had metastatic isease at the time of initial diagnosis. Four patients were free rom disease at 19–133 months' follow-up. All had encapsulated umours. Patients with locally infiltrating tumours were at high isk for disease recurrence. Encapsulated tumours should lways be excised and solitary infiltrating lesions require an xtended resection. This approach is not justified for multiple infiltrating or metastatic paraganglioma, when tumour reduction may be considered.

Hyperparathyroidism as part of the MEN IIA syndrome is usually caused by benign parathyroid adenoma. Parathyroid carcinoma is a rare cause of hyperparathyroidism, although an incidence of malignancy of up to 5 per cent has been reported in patients with hyperparathyroidism from Japan. Bartsch *et al.*[4] from Marburg report experience with three patients presenting with parathyroid carcinoma treated between 1978 and 1992 at two institutions. During the same period, 658 patients underwent surgery for primary hyperparathyroidism. The authors indicate that a diagnosis of parathyroid carcinoma should be reserved for patients with clinical signs of malignancy such as local recurrence or distant metastases, and that a diagnosis based on histological criteria alone may not be reliable. Clinical signs of malignancy include a palpable mass in the neck and intraoperative findings of a grey-white dense mass surrounded by a capsule of fibrous tissue. The authors recommend surgical *en bloc* resection including the ipsilateral thyroid lobe and isthmus, pretracheal soft tissue, tracheo-oesophageal lymph nodes and lymph nodes of the carotid–jugular vascular sheath as initial treatment. This may result in a long disease-free interval. Chemotherapy or radiation therapy is largely ineffective.

Rectal cancer

Preoperative staging of rectal carcinoma is important to formulate surgical or combined treatment. Kipfmüller *et al.*[5] from Stuttgart prospectively evaluated endosonography and magnetic resonance imaging (MRI) for preoperative staging of rectal cancer. Forty-four patients with rectal tumours were studied and pathological staging of surgical specimens compared with results of preoperative diagnosis. Only local infiltration of the rectal wall was studied and no attempt was made to identify metastatic pararectal lymph nodes. Five patients had adenoma, three T_1 carcinoma, 17 T_2 carcinoma, 16 T_3 carcinoma and three T_4 rectal carcinoma. Clinical staging (Mason) was possible in 34 of the 44 patients; the tumour could not be reached in ten. A correct diagnosis was made in 29 tumours, with only two being understaged. Forty-one tumours were studied by endosonography; three could not be evaluated because of severe stenosis. Three tumours were understaged and four overstaged, giving a diagnostic accuracy of 83 per cent. Studies by MRI could not detect two of eight $T_{0/1}$ tumours and two of 33 $T_{2/3}$ lesions. Eleven tumours were understaged, giving an overall diagnostic accuracy of only 54 per cent. The authors conclude that rectal ultrasonography is superior to MRI for the determination of local infiltration, particularly of rectal adenoma and T_1 carcinoma.

Malignant melanoma

Although the incidence of malignant melanoma of the extremities in the Western world continues to rise, the range of treatments available has been increased by using techniques to deliver high doses of potent chemotherapeutic drugs locally. Henneking and colleagues[6] from Gießen report results of isolated hyperthermic extremity perfusion in 451 patients with

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malignant melanoma treated between October 1979 and September 1989. The surgical technique remained essentially the same during this period, but the chemotherapeutic agents used varied. The dose of drug administered was adjusted according to the volume of the extremity. The majority of patients were treated with melphalan (10 mg/l) alone or in combination with either actinomycin (0·1 mg/l) or cisplatin (15 mg/l). The perfusion temperature was 41°C (or 39·5°C for cisplatin). A detailed description of clinical and histological criteria is provided. Some 259 patients were classed as M. D. Anderson stage I, i.e. had primary tumours without satellite, in-transit, lymph node or distant metastases. Three patients died in the postoperative period. Three further patients required extremity amputation. Other postoperative complications included delayed wound healing (26·3 per cent), wound seroma (8·4 per cent), lymph fistula (9·1 per cent), bleeding (1·8 per cent) and deep vein thrombosis (1·3 per cent). Persistent lymphoedema was recorded in 12·3 per cent. Irreversible sensory and motor neurological defects were observed in 9·1 and 7·3 per cent of patients respectively. All patients were followed for a mean of 59 months. The 5-year survival rate was 64 per cent for all patients. The 5-year survival rate was 80–87 per cent for melanoma of the upper extremity and 44–65 per cent for lesions of the lower extremity. Survival was related to tumour thickness, with an 84 per cent 5-year survival rate for lesions of 0·76–1·50 mm and 47 per cent for those >4 mm thick. Similar results were obtained for Clark levels III (75 per cent), IV (70 per cent) and V (46 per cent). Survival rates according to M. D. Anderson stage were 85 per cent (stage I), 48 per cent (stage II), 31 per cent (stage IIIA), 52 per cent (stage IIIB) and 15 per cent (stage IIIAB). Multivariate analysis of prognostic parameters using the proportional hazards model revealed prognostic significance for M. D. Anderson stage, tumour thickness, superficial spreading melanoma and localization. No prognostic significance could be demonstrated for Clark level or sex. The authors conclude that hyperthermic isolated extremity perfusion should be performed in tumour node metastasis (TNM) stages II and III whereas, in TNM stage I, local excision with a recommended margin of 3 cm for pT_2 tumours is sufficient. In patients with distant metastases hyperthermic limb perfusion may be used for palliation.

Carcinoma of the pancreas

Improved perioperative management has successfully reduced the mortality rate after extended resection for carcinoma of the pancreas. Long-term survival has, however, not been improved. Intraoperative radiotherapy has been used in patients with carcinoma of the pancreas to improve local control of the tumour. Kasperk *et al.*[7] from Aachen report initial experience with 23 patients with pancreatic cancer treated by intraoperative radiotherapy between 1989 and 1991. Intraoperative radiation was administered with an average dose of 20 Gy. During the same period 36 patients were treated without additional intraoperative radiotherapy. Allocation to each treatment group was determined by intraoperative conditions. Patients with extensive intra-abdominal tumour spread or those unfit for transport to the radiotherapy unit (10 min) were excluded from intraoperative radiotherapy and no randomization wa attempted. Potentially curative resection was performed in seven of 23 patients in whom intraoperative radiotherapy wa administered. Twelve patients had only palliative operation ($R_{1/2}$ resection or bypass procedure) and four underwen laparotomy only. No operative complications of intraoperative radiotherapy were recorded. The 30-day mortality rate o patients receiving intraoperative radiotherapy (two of 23) was comparable to that of those not given radiotherapy (four o 36). Severe postoperative complications such as pancreatic fistula, anastomotic leakage, abscess formation or pancreatitis occurred more frequently in patients given radiotherapy (seven of 23) than in those not (three of 36). The postoperative hospital stay was 32 days in patients receiving intraoperative radiotherapy compared with 26 days in those not. The postoperative survival time was lower in patients given radiotherapy. After R_0 resection the average postoperative survival time of patients given radiotherapy was 320 days compared with 366 days for those without. In patients treated palliatively, survival was 89 days when intraoperative radiotherapy was administered and 189 days when it was not used These results indicate an adverse effect of radiotherapy but the authors believe that a combination of radiotherapy with chemotherapy will improve treatment results, since four of six patients receiving postoperative 5-fluorouracil chemotherapy (500 mg/m^2) in addition to intraoperative radiotherapy were alive at 6–11·5 months.

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Foot volumetry and duplex ultrasonography after saphenous and subfascial perforating vein ligation for recurrent venous ulceration

Forty-three patients undergoing superficial and perforating vein ligation for recurrent venous ulceration underwent preoperative and postoperative foot volumetry and postoperative duplex ultrasonography. Patients were followed for a median of 66 (range 18–144) months. Of nine patients who developed recurrent ulceration, six had femoral vein incompetence and all had popliteal vein incompetence demonstrated by duplex ultrasonography. Of the 34 patients who remained ulcer-free, five had femoral vein incompetence and a single patient had popliteal vein incompetence on duplex scanning, giving positive predictive values for recurrent ulceration of 55 per cent (femoral vein incompetence) and 90 per cent (popliteal vein incompetence). Patients with saphenofemoral incompetence on late follow-up were also more likely to suffer recurrence. Preoperative foot volumetry with tourniquet occlusion of superficial veins showed that the median expulsion fraction of patients who developed recurrent ulcer during follow-up was 0·8 (range 0·6–2·3) per cent compared with 1·5 (range 0·4–2·9) per cent for those who remained ulcer-free ($P = 0{\cdot}025$); the median half-refilling time of patients with recurrent ulcer was 1·5 (range 0·5–5·5) s compared with 5·0 (range 0·5–23·0) s for those without recurrence ($P < 0{\cdot}01$). Postoperative foot volumetry showed similar differences. Deep venous incompetence, particularly of the popliteal segment, as demonstrated by duplex ultrasonography and foot volumetry, is a useful predictor of recurrent ulceration after subfascial perforator and superficial venous ligation.

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Although most patients with venous ulceration are successfully managed by compression bandaging and elevation, a proportion require surgery[1,2]. Direct ligation of perforators, combined with ligation of veins at other sites of deep to superficial reflux, remains the most popular operation and leads to permanent ulcer healing in 57–98 per cent of patients[3–12]. Nevertheless, a number of surgical procedures, including valve reconstruction, venovenous bypass and axillary vein transplantation, have been performed in the belief that deep venous incompetence plays an equally important role in the pathogenesis of chronic venous insufficiency[13,14].

Although studies indicate that fewer than one-third of all patients with chronic venous ulceration have significant deep venous incompetence, in 80 per cent of these patients incompetence includes the popliteal vein[15–20]. This so-called 'gatekeeper' segment appears to have a particularly important role in maintaining a normal haemodynamic and clinical state[21]. It is, therefore, possible that the importance of deep venous reflux has been underestimated in these patients and, further, that such deep reflux will render simple deep to superficial venous ligation inadequate as a means of achieving permanent ulcer healing.

The aim of the present study was to relate recurrent ulceration following subfascial perforator and superficial vein ligation with haemodynamic abnormalities, particularly deep and superficial venous incompetence, as determined by foot volumetry and duplex ultrasonography.

Patients and methods

The series comprised 43 patients, 23 men (mean age 53 (range 41–64) years) and 20 women (mean age 56 (range 30–70) years), who underwent subfascial ligation of perforating veins for venous ulceration. Subfascial ligation was performed because the leg was felt to be too chronically inflamed and scarred to be amenable to direct perforator dissection and ligation. Perforator ligation was performed in addition to saphenopopliteal and/or saphenofemoral ligation in patients who had superficial venous reflux on clinical examination. None of the patients had an arterial component to the ulceration as determined by clinical examination and ankle:brachial pressure index.

All patients had suffered recurrent episodes of ulceration over a prolonged period (up to 20 years) and, despite a carefully conducted outpatient and/or inpatient regimen of conservative treatment including elevation, compression bandaging and injection sclerotherapy, had failed to gain sustained ulcer healing. Although, as is the surgical policy in the authors' unit, all ulcers were healed at the time of surgery, this had in most cases required a period of inpatient bed-rest with elevation and/or skin grafting. This series of patients therefore represents the severe end of the disease spectrum.

Operations were performed between 1979 and 1986 under the care of a single surgeon (C.V.R.). Once other proximal sites of incompetence had been dealt with, a posterior–medial stocking-seam incision was used under tourniquet control. In the lower two-thirds of the calf the incision was taken to one or other side of the Achilles tendon, depending on whether the principal perforators were medially or laterally placed. All medial and lateral perforators (ranging from one to five) were divided under direct vision. After operation patients were routinely prescribed below-knee graduated compression stockings.

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Patients were followed monthly for 3 months, then at intervals of 6 months for a median of 66 (range 18–144) months. They underwent preoperative foot volumetry, with and without tourniquet occlusion of superficial veins, as previously described[22]. Foot volumetry was also performed after operation. Total foot volume was measured as was the expelled volume after exercise consisting of 20 knee-bends. The expulsion fraction was defined as the percentage of expelled volume relative to total foot volume. Half-refilling time was defined as the time taken for the foot to return half-way to its pre-exercise volume. Tourniquet tests were performed with a below-knee narrow-gauge (4-cm) tourniquet applied at a pressure of 100–150 mmHg depending on the patient's height. Duplex ultrasonography became available in 1987, after which patients underwent duplex examination to document the presence of deep and superficial vein incompetence within the superficial femoral, popliteal, long saphenous and short saphenous veins.

Duplex ultrasonography was performed with an Acuson 128 machine (Acuson, Mountain View, California, USA) using either a 5-MHz or 7·5-MHz transducer. Patients were examined in a 30° head-up tilt and standing, and tourniquets were used to clarify the patterns of refux in a manner similar to the Trendelenburg test. Venous incompetence was also assessed by means of a Valsalva manoeuvre and distal calf compression. Incompetence was defined as reverse flow lasting > 2 s in the standing position. The median time between surgery and duplex ultrasonography was 52 (range 12–120) months.

Results

Duplex ultrasonography

Nine patients developed a recurrent ulcer during the follow-up period (median 84 (range 24–144) months) (*Table 1*). These ulcers occurred at a median of 42 (range 3–131) months after surgery. Six of the patients had superficial femoral vein incompetence and all had popliteal vein incompetence on duplex ultrasonography. By contrast, of the 34 patients who did not develop recurrent ulceration during follow-up (median 60 (range 18–131) months), five had femoral vein incompetence and only one popliteal vein incompetence. Popliteal and femoral vein incompetence, therefore, allow identification of patients likely to suffer recurrent ulceration following subfascial perforator and superficial venous ligation with positive predictive values of 90 and 55 per cent respectively. Two patients with recurrent ulceration had short saphenous vein incompetence. A single patient who did not have a recurrent ulcer but who did have popliteal vein incompetence did not have associated short saphenous vein incompetence. The saphenofemoral junction was not visualized by duplex ultrasonography because of previous saphenofemoral ligation in 21 patients. In a further 15 patients the saphenofemoral junction and long saphenous vein were visualized and found to be competent. In seven patients the saphenofemoral junction had not been ligated at surgery and was found to be incompetent on duplex ultrasonography. Four of these seven patients developed further ulceration compared with only five of the 36 in whom the saphenofemoral junction had been ligated or was identified as competent.

Table 1 *Relationship between venous incompetence and recurrent ulceration after subfascial ligation of perforators in 43 patients*

	Recurrent ulcer	No recurrent ulcer
Short saphenous vein		
Incompetent	2	9
Competent or ligated	7	25
Long saphenous vein		
Incompetent	4	3
Competent or ligated	5	31
Femoral vein		
Incompetent	6	5
Competent	3	29
Popliteal vein		
Incompetent	9	1
Competent	0	33

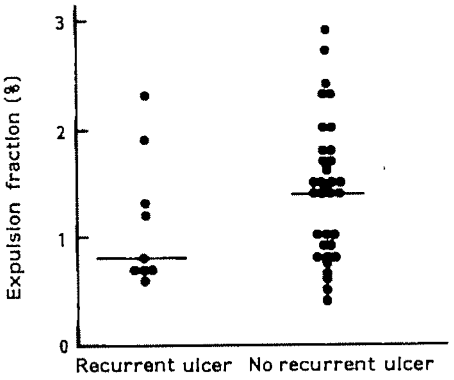


Figure 1 *Preoperative expulsion fraction in the presence of superfici tourniquet occlusion in patients developing recurrent ulcer and in tho remaining ulcer-free. Bars are median values.* P = 0·025 (*Wilcoxon signe rank test*)

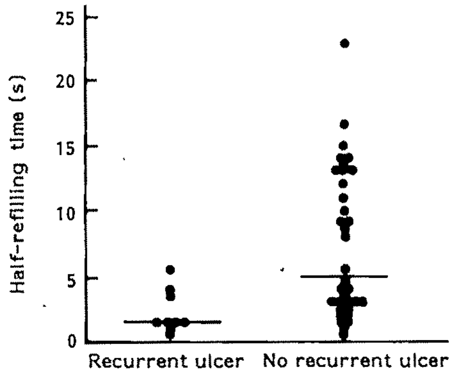


Figure 2 *Preoperative half-refilling time in the presence of superfici tourniquet occlusion in patients developing recurrent ulcer and in thos remaining ulcer-free. Bars are median values.* P < 0·01 (*Wilcoxon signe rank test*)

Table 2 *Foot volumetry performed before and after operation wit tourniquet occlusion of superficial veins*

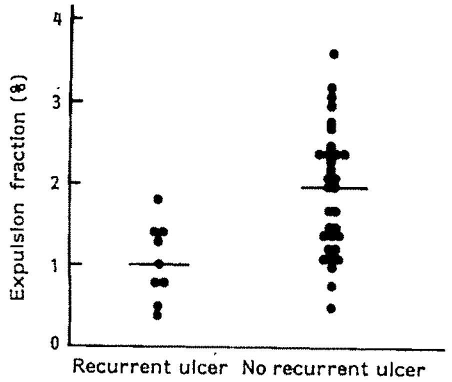
	Recurrent ulcer ($n = 9$)		No recurrent ulcer ($n = 34$)	
	Expulsion fraction (%)	Half-refilling time (s)	Expulsion fraction (%)	Half-refilling time (s)
Before operation	0·8 (0·6–2·3)	1·5 (0·5–5·5)	1·5 (0·4–2·9)	5·0 (0·5–23·0
After operation	1·0 (0·4–1·8)	3·0 (1·0–4·5)	2·0 (0·5–3·6)	10·5 (1·5–19·5

Values are median (range)

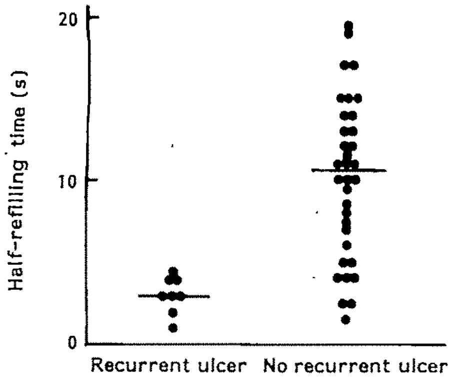
Table 3 *Foot volumetry performed before and after operation withou tourniquet occlusion of superficial veins*

	Recurrent ulcer ($n = 9$)		No recurrent ulcer ($n = 34$)	
	Expulsion fraction (%)	Half-refilling time (s)	Expulsion fraction (%)	Half-refilling time (s)
Before operation	1·4 (0·6–3·0)	4·7 (1·3–21·5)	1·1 (0·2–3·1)	3·6 (1·3–17·5)
After operation	1·7 (0·8–4·5)	5·5 (1·7–20·5)	2·0 (0·7–4·4)	6·0 (2·5–24·5)

Values are median (range)



igure 3 *Postoperative expulsion fraction in the presence of superficial urniquet occlusion in patients developing recurrent ulcer and in those maining ulcer-free. Bars are median values.* $P < 0.05$ *(Wilcoxon signed nk test)*



igure 4 *Postoperative half-refilling time in the presence of superficial ourniquet occlusion in patients developing recurrent ulcer and in those emaining ulcer-free. Bars are median values.* $P < 0.02$ *(Wilcoxon signed nk test)*

oot volumetry

When foot volumetry was performed before operation in the presence of tourniquet occlusion of superficial veins, the xpulsion fraction and half-refilling time of patients who developed recurrent ulceration were significantly lower than hose of patients who remained ulcer-free ($P < 0.03$, Wilcoxon igned rank test) (*Figures 1* and *2*; *Table 2*). When foot olumetry was performed without superficial vein tourniquet occlusion, there was no such difference (*Table 3*). When foot volumetry with tourniquet occlusion of superficial veins was performed after operation, both the expulsion fraction and half-refilling time were also significantly higher in the patients who remained ulcer-free ($P < 0.05$, Wilcoxon signed rank test) *Figures 3* and *4*; *Table 2*). Again, when foot volumetry was performed without a tourniquet, there was no difference between patients who developed recurrent ulceration and those who remained ulcer-free (*Table 3*).

Discussion

Although the majority of venous ulcers can be healed by an outpatient regimen of graduated compression bandaging and elevation, or less commonly by an inpatient regimen of elevation and bed-rest, many of these ulcers will recur. Thus, in the Lothian and Forth Valley survey, 66 per cent of 600 patients studied had suffered multiple episodes of venous ulceration over a 5-year period[23]. Even when patients are fully compliant and committed to optimal conservative treatment[24], up to 29 per cent of ulcers return within 5 years. In an attempt to reduce such recurrence, surgeons have advocated ligation of perforating veins, with or without saphenous ligation, for recurrent and, in some cases, primary venous ulcers[25]. Disappointingly, however, despite such surgery, recurrence rates of up to 55 per cent have been reported, and subfascial ligation is not without its complications[26]. For these reasons it would be of great benefit to be able to identify, before operation, patients who are unlikely to achieve a good long-term result from subfascial perforator ligation in combination with saphenous ligation, especially if this could be achieved by means of a non-invasive test.

The non-invasive assessment of chronic venous insufficiency has become part of the standard armamentarium of the specialist vascular surgeon and can provide detailed information on the functional and anatomical status of both the superficial and deep venous systems[27,28]. Of the techniques available, duplex ultrasonography and foot volumetry are of recognized value[29,30]. In the present study of 43 patients undergoing subfascial ligation, with saphenopopliteal and/or saphenofemoral ligation as appropriate in the presence of clinically detectable saphenous incompetence, for recurrent venous ulcer and followed for a median of 66 months, there were nine with recurrent ulcers with a median duration to onset of 42 months. This is similar to the reports of others[3–13]. The presence of femoral and popliteal deep vein reflux identified patients developing recurrent ulcer with positive predictive values of 55 and 90 per cent respectively. Thus it appears, even following ligation at sites of deep to superficial incompetence, that an intact and competent popliteal vein is required to prevent recurrent ulceration[31]. The addition of saphenopopliteal ligation to subfascial ligation did not affect the rate of recurrent ulceration, although the proportion of patients with such reflux was small. At the time of surgery, 21 patients had saphenofemoral incompetence on clinical examination and had saphenofemoral ligation performed in addition to perforator ligation; three of these patients suffered further ulceration after operation. Of the 22 patients thought not to have saphenofemoral incompetence at the time of surgery, postoperative duplex ultrasonography confirmed competence in 15 but showed reflux in the remaining seven. It is not known whether this saphenofemoral incompetence developed after surgery in these patients or whether it had not been detected at the original preoperative examination. Importantly, however, four of these seven patients had failed to gain permanent ulcer healing from perforator ligation alone. By comparison, of the 15 patients with a competent saphenofemoral junction after operation, only two had further ulceration. This confirms the importance of eradicating saphenofemoral incompetence in patients with venous ulceration[25,32].

There was a significant difference in median expulsion fraction and half-refilling time, as demonstrated by both preoperative and postoperative foot volumetry with superficial tourniquet occlusion, between patients who developed recurrent ulceration and those who remained ulcer-free during follow-up. Foot volumetry with tourniquet occlusion of superficial veins therefore reflects the findings of duplex ultrasonography and further confirms the importance of deep venous incompetence in the pathogenesis of further ulceration after surgery. However, despite the presence of statistical significance, the overlap between the results obtained in the two groups, particularly with respect to expulsion fraction, casts doubt on the ability of foot volumetry to distinguish patients with sufficient accuracy before surgery, and suggests that duplex scanning is the more useful of the two methods. Foot volumetry performed without superficial vein occlusion was of no value, and results were difficult to interpret because of the combined effects of superficial and deep venous reflux in individual patients.

In summary, subfascial ligation combined with correction of saphenous incompetence where clinically detected was successful in preventing further ulceration in 34 of the 43 patients studied. All patients who developed recurrent ulceration had popliteal vein incompetence demonstrated by duplex ultrasonography, compared with only one patient in the permanently healed group. The importance of deep venous reflux in patients with recurrent ulceration was also confirmed by the results of foot volumetry. This study demonstrates that patients with popliteal vein incompetence do not gain good results from perforator ligation alone and we suggest that they either be managed conservatively or be considered for reconstructive deep venous surgery. With respect to superficial venous incompetence, 44 per cent of patients with saphenofemoral reflux suffered further recurrence compared with only 9 per cent of those in whom the saphenofemoral junction was intact or had previously been treated. Thus, even when superficial venous reflux is not present initially, it is important to treat it if and when it arises.

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Recurrent varicose veins: correlation between preoperative clinical and hand-held Doppler ultrasonographic examination, and anatomical findings at surgery

A consecutive series of 118 patients (148 legs) presenting with recurrent varicose veins underwent preoperative clinical and hand-held Doppler ultrasonographic examination by a single observer. The presence of saphenofemoral, mid-thigh perforator and saphenopopliteal reflux was noted. Ultrasonography markedly improved the accuracy of clinical assessment at all three potential sites of reflux compared with operative findings. Of 71 patients undergoing repeat groin dissection, only 20 (28 per cent) had a tied saphenofemoral junction, 31 (44 per cent) had intact major tributaries and 52 (73 per cent) had an intact long saphenous vein (LSV) in the thigh. There was a positive association between mid-thigh perforator reflux giving rise to recurrent varices and the presence of an intact LSV in the thigh. Of 45 legs with saphenopopliteal reflux, only four had previously undergone saphenopopliteal ligation, suggesting that most short saphenous varicosities had either appeared after or had not been recognized at the time of primary surgery. This study indicates that even an experienced vascular surgeon can have difficulty in assessing the presence or absence of recurrent deep to superficial reflux by means of clinical examination alone and that Doppler ultrasonographic examination is mandatory. Recurrence continues to be associated with persistent or recurrent incompetence at the site of previous inadequate surgery.

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Vhen performed correctly, flush saphenofemoral ligation with bove-knee long saphenous vein (LSV) stripping for primary ncomplicated long saphenous varicose veins is an excellent peration[1–3]. Unfortunately, up to 25 per cent of patients who ave undergone such surgery will develop recurrent varices in he long saphenous territory[4–6]. For example, the Lothian urgical audit database[7,8] has shown that, of 1014 consecutive aricose vein operations undertaken in the region between 1 anuary and 31 December 1990, approximately 20 per cent ere performed for recurrent disease. Although recurrence may e due to direct connections with pelvic veins, it more ommonly arises from a failure to perform an adequate aphenofemoral ligation and obliteration of the LSV at the first peration[9,10]. Correct management of recurrent varices epends on accurate preoperative assessment of the anatomy esponsible. The aim of the present study was to analyse the attern of recurrent varicosities in a large consecutive series of atients presenting to a single surgeon and to correlate reoperative assessment with anatomical findings at operation.

atients and methods

he series comprised 148 legs of 82 women (mean age 52 years) and 6 men (mean age 50 years) presenting to and operated on by a single urgeon (C.V.R.). Recurrent disease was present on the left side in 72 gs and on the right side in 76. Bilateral disease was present in 31 atients (three men, 28 women).

All patients underwent preoperative clinical and hand-held Doppler ltrasonographic examination by a single observer (C.V.R.). To date, 1 patients have undergone repeat surgery that included redissection f the groin. At operation the saphenofemoral junction (SFJ) was pproached from the lateral side by exposing the common femoral rtery[11,12]. The presence or absence of saphenofemoral, mid-thigh perforator, saphenopopliteal and calf perforator reflux was noted before operation. At operation the presence or absence of an intact SFJ, major tributaries and a patent LSV in the thigh was noted. The SFJ was described as intact if, after exposure of the common femoral artery, the upper 3 cm or more of the LSV was found to be patent. Sometimes the entire vein in the groin was intact; more commonly it was embedded in scar tissue and its connection with more peripheral veins could not be fully dissected out. The LSV was described as intact if it was found to be present for most of its length in the thigh. Major tributaries in the groin (superficial external pudendal, superficial circumflex iliac or superficial inferior epigastric veins) were described as present when found to be patent and still connected to the SFJ or to the upper end of the LSV.

Results

Past medical history

Twenty-five patients (21 men, four women) had previously suffered deep vein thrombosis of the affected leg. Twelve patients (nine men of mean age 55 years, three women of mean age 64 years) had previously suffered a varicose ulcer of the affected leg. Some 97 legs had undergone one previous operation for varicose veins; 35 legs had undergone two, 14 had undergone three and two had undergone four previous operations. A total of 120 legs had undergone a previous saphenofemoral tie, 12 had undergone previous saphenopopliteal ligation and 16 had had avulsion only.

Clinical and Doppler ultrasonographic examination in the assessment of the saphenofemoral junction (Table 1)

The relationship between the findings of clinical and hand-held Doppler ultrasonographic examination with respect to the presence or absence of saphenofemoral reflux in patients with

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Table 1 *Relationship between clinical and hand-held Doppler ultrasonographic examination and the presence or absence of saphenofemoral reflux in 148 limbs*

Saphenofemoral reflux on Doppler ultrasonographic examination	Saphenofemoral reflux on clinical examination		
	Present (*n*=66; 45%)	Absent (*n*=33; 22%)	Unclear (*n*=49; 33%)
Present (*n* = 100; 68%)	63	5	32
Absent (*n* = 42; 28%)	1	27	14
Unclear (*n* = 6; 4%)	2	1	3

Table 2 *Relationship between anatomical findings at repeat groin dissection and preoperative assessment by clinical examination in 71 limbs*

	Saphenofemoral reflux on clinical examination		
Operative findings	Present	Absent	Unclear
Intact saphenofemoral junction (*n* = 51)	37	2	12
Tied saphenofemoral junction (*n* = 20)	4	5	11
Major tributaries intact (*n* = 31)	17	2	12
Long saphenous vein intact (*n* = 52)	27	5	20

Table 3 *Relationship between anatomical findings at repeat groin dissection and preoperative assessment by Doppler ultrasonographic examination in 71 limbs*

	Saphenofemoral reflux on Doppler ultrasonographic examination		
Operative findings	Present	Absent	Unclear
Intact saphenofemoral junction (*n* = 51)	47	3	1
Tied saphenofemoral junction (*n* = 20)	9	10	1
Major tributaries intact (*n* = 31)	23	7	1
Long saphenous vein intact (*n* = 52)	41	10	1

Table 4 *Relationship between clinical and hand-held Doppler ultrasonographic examination and the presence or absence of mid-thigh perforator reflux in 148 limbs*

Mid-thigh perforator reflux on Doppler ultrasonographic examination	Mid-thigh perforator reflux on clinical examination		
	Present (*n*=31; 21%)	Absent (*n*=63; 43%)	Unclear (*n*=54; 36%)
Present (*n* = 45; 30%)	21	2	22
Absent (*n* = 89; 60%)	6	61	22
Unclear (*n* = 14; 9%)	4	0	10

recurrent varicose veins is shown in *Table 1*. In one-third of cases the surgeon was uncertain on clinical examination alone about the presence of saphenofemoral incompetence. By contrast, there was uncertainty after Doppler ultrasonographic examination in only six legs. Otherwise there was good agreement between the two methods.

Anatomical findings in relation to preoperative assessment (Tables 2 *and* 3)

To date, 71 patients with recurrent varicose veins emanati from the groin have undergone repeat groin exploration. these, 51 (72 per cent) had an intact SFJ and only (28 per cent) had a tied SFJ. In addition, of these 71 patien 31 (44 per cent) had intact major tributaries feeding into eith an intact LSV stump or an intact LSV in the thigh. In patients (73 per cent) the LSV was intact throughout most the length of the thigh. There was a better association betwe an intact SFJ and saphenofemoral reflux on Doppl ultrasonographic than on clinical examination alone.

Mid-thigh perforator reflux (Tables 4 *and* 5)

Whereas there was doubt about the presence of a mid-thi perforator on clinical examination alone in one-third of case there was doubt in fewer than 10 per cent of cases when Doppl ultrasonography was used. There was a positive associatio between mid-thigh perforator reflux giving rise to recurre varices and the presence of an intact LSV in the thigh.

Saphenopopliteal reflux (Table 6)

Whereas there was doubt about saphenopopliteal reflux one-fifth of cases after clinical examination, there was no dou in the surgeon's mind following Doppler ultrasonography. the 45 legs in which saphenopopliteal reflux was detected Doppler ultrasonographic examination, only four had previous undergone saphenopopliteal ligation. Thus, most sho saphenous varices had either appeared after initial surgery had not been recognized as stemming from the short saphen system at the time of the initial operation.

Calf perforator reflux (Table 7)

The majority of patients had calf perforator reflux, which w detected equally well on clinical and on Doppler ultrason graphic examination.

Table 5 *Relationship between mid-thigh perforator reflux and an inta long saphenous vein in the thigh at repeat groin dissection in 71 limbs*

Mid-thigh perforator reflux on	Long saphenous vein intact (*n* = 52)	Long saphenou vein previously stripped (*n* = 1
Doppler ultrasonographic examination		
Present	21	2
Absent	28	15
Unclear	3	2
Clinical examination		
Present	12	3
Absent	14	11
Unclear	26	5

Table 6 *Relationship between clinical and hand-held Doppl ultrasonographic examination and the presence or absence saphenopopliteal reflux in 148 limbs*

Saphenopopliteal reflux on Doppler ultrasonographic examination	Saphenopopliteal reflux on clinical examinatio		
	Present (*n*=33; 22%)	Absent (*n*=86; 58%)	Unclear (*n*=29; 20%
Present (*n* = 45; 30%)	27	8	10
Absent (*n* = 103; 70%)	6	78	19

There were no limbs in which ultrasonographic examination gav unclear results ble 7 *Relationship between clinical and hand-held Doppler rasonographic examination and the presence or absence of calf forator reflux in 148 limbs*

lf perforator flux on Doppler rasonographic amination	Calf perforator reflux on clinical examination		
	Present (n=117; 79%)	Absent (n=27; 18%)	Unclear (n=4; 3%)
esent (n = 111; 75%)	108	1	2
sent (n = 32; 22%)	5	26	1
nclear (n = 5; 3%)	4	0	1

iscussion

ecurrent varicose veins are a common clinical problem presenting a major burden to patients and surgeons alike. orrect management of the problem depends on accurate sessment of the underlying anatomy. The present study dicates that even an experienced vascular surgeon can have fficulty in assessing the presence or absence of deep to perficial reflux at the level of the groin, mid-thigh and opliteal fossa by means of clinical examination alone. There no doubt that hand-held Doppler ultrasonographic camination improves the overall accuracy of preoperative sessment in the presence of primary varices[13–17]. The present udy indicates that this is equally so in the presence of recurrent arices[5]. Despite this, doubt will remain in a small proportion f cases and the surgeon must then either operate 'blind' or sort to other imaging techniques such as varicography.

This study has also clearly demonstrated that recurrence is redominantly associated with persistent or recurrent incometence at the SFJ associated with an intact SFJ, intact major ibutaries and/or an intact LSV in the thigh. These errors can e avoided by making an adequate incision, ligating tributaries eyond their first branch points and ensuring a flush ligation f the SFJ. In addition, the LSV should be removed to knee vel to deal with the mid-thigh perforator[18].

In conclusion, this study confirms that, despite the onsiderable literature on the subject, a significant proportion f the surgery carried out for primary uncomplicated varicose eins is inadequate. Faulty surgical technique is the major cause f recurrent varicose veins.

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For debate

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Vein-patch rupture after carotid endarterectomy: an avoidable catastrophe

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After carotid endarterectomy, vein-patch angioplasty confers several advantages over primary arterial closure, and arteriotomy closure with a vein patch has become commonplace[1]. Rupture of the patch is a recognized, although infrequent, complication after such closure, with potentially disastrous consequences for the patient. The authors have recently experienced another instance of carotid vein-patch blowout. Having examined current regional trends in carotid endarterectomy practice with respect to closure technique, we believe that wider recognition of this largely avoidable catastrophe is warranted.

A 62-year-old man underwent elective right carotid endarterectomy, having presented with a 3-month history of recurrent right carotid territory transient ischaemic events. Carotid angiography showed 70 per cent stenosis of the right and 50 per cent stenosis of the left internal carotid artery, and computed tomography of the brain revealed a small right medial basal ganglion infarct. At operation, the origin of the right internal carotid artery was found to be occluded by a plaque, with intraplaque haemorrhage; using a Javid shunt, a satisfactory endarterectomy was achieved and the arteriotomy closed with a portion of ankle saphenous vein. The patient remained normotensive and appeared to be making a satisfactory recovery until 3 days after operation when sudden massive haemorrhage from the neck wound led to emergency exploration. Control of bleeding was achieved by caro clamping and a split was discovered in the central portion the vein patch; the suture line was intact and there was evidence of infection. A Javid shunt was inserted and the caro artery repaired with a polytetrafluoroethylene patch. T patient suffered an intraoperative myocardial infarction a cardiac arrest, from which he was successfully resuscitated, a a right hemisphere stroke causing left hemiparesis a dystharthria. However, the neurological signs improv substantially, such that the patient was discharged home 9 da later; he displayed only minor weakness in the left hand follow-up at 2 months.

Since 1989, all patient discharges from Scottish hospit after carotid surgery have carried separate diagnostic data cod for carotid endarterectomy with primary arterial closure a with patch angioplasty. Examination of the computer recor (SMR1 and MOR 2271 discharge data files) for the 279 caro endarterectomies performed during the years 1989–19 revealed a definite trend in closure technique. There was a 1 per cent increase in the annual number of carot endarterectomies, from 65 in 1989 to 143 in 1991, with t proportion followed by patch angioplasty closure rising fro seven (11 per cent) to 46 (32 per cent). Information on t nature of the patch or, in the case of a vein patch, its sour was not available. There were three deaths during this 3-ye period (1·1 per cent operative mortality rate).

Vein-patch closure after carotid endarterectomy has gain widespread, although not universal, popularity, in the hope improving postoperative patency, reducing the risk thrombosis and avoiding late restenosis, especially in patien with small-calibre vessels. Although the type of patch materi used is not explicitly defined in the computer discharge codin we believe that there is a trend toward the increasing use vein. This concurs with the changes in carotid endarterecto practice in Great Britain and Ireland reported by Murie a Morris[1] in their survey of 1989 data, in which the use prosthetic patch material was noted to be rare.

Postoperative rupture of the vein patch is said to be a ra event, with several large series[2–4] reporting incidences 0·4–0·7 per cent. However, rupture is probably an unde reported complication[2]; a comprehensive review of t literature to date reveals a total of 38 reported instances vein-patch blowout[2–10] (*Table 1*) from which several consiste

Table 1 *Summary of 38 reported cases of vein-patch rupture after carotid endarterectomy*

Reference	No. of cases	Vein site	Time of rupture	Outcome
Tawes and Treiman[2]	13	Ankle ($n = 12$) Groin ($n = 1$)	Day 1 ($n = 2$) Day 2 ($n = 6$) Day 3 ($n = 3$) Day 8 ($n = 1$) Day 21 ($n = 1$)	Fatal ($n = 4$) Stroke ($n = 3$) Retinal embolus ($n = 1$) Full recovery ($n = 5$)
Van Damme *et al.*[3]	2	Ankle	Days 5 and 7	Fatal ($n = 2$)
O'Hara *et al.*[4]; Hertzer *et al.*[10]	8	Lower leg	Day 1 ($n = 4$) Days 2–5 ($n = 4$)	Fatal ($n = 1$) Stroke ($n = 1$) Full recovery ($n = 6$)
Riles *et al.*[5]	3	Ankle	Days 2–5	Full recovery ($n = 3$)
Katz *et al.*[6]	3	Ankle	<72 h	Stroke ($n = 2$) Full recovery ($n = 1$)
Eikelboom *et al.*[7]	4	Not stated	Day 2 ($n = 1$) (Others not stated)	Stroke and recovery ($n = 1$ (Others not stated)
Bartlett *et al.*[8]	2	Not stated	Not stated	Stroke ($n = 1$) Full recovery ($n = 1$)
Archie and Green[9]	2	Ankle	During operation ($n = 1$) Day 5 ($n = 1$)	Full recovery ($n = 2$)
Present paper	1	Ankle	Day 3	Stroke

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tures are apparent. Carotid vein-patch rupture character- cally presents as massive haemorrhage, asphyxia or urological deficit associated with a rapidly enlarging cervical ematoma within 5 days (in 91 per cent of cases) of carotid darterectomy. It is an aseptic rupture through an area of crosis in the centre of the vein patch, distinct from the suture e. The most striking feature is that rupture occurs almost clusively in veins harvested from the ankle or lower leg 7 per cent), and a high incidence of vein-patch rupture of er cent has been cited in a series of 75 consecutive carotid darterectomies in which ankle vein was used exclusively[5], th only one reported example of rupture of a patch made m groin vein[2]. Carotid vein-patch blowout carries a bstantial morbidity and mortality rate, proving fatal in seven 35 reported cases and causing stroke with residual disability a further nine. Uncontrolled hypertension in the post- erative period appears to be associated with vein-patch pture; this is supported by experimental evidence that eoperative diagnosis of hypertension (as well as female sex, vanced age and diabetes) diminishes the physical strength of wer leg saphenous vein measured *in vitro*[11]. It may also be nificant, therefore, that no fewer than 17 of 24 cases of in-patch rupture occurred in women.

Although further evidence from biomechanical studies of fferences in rupture pressure between veins harvested from e groin, knee and ankle is lacking[9,12], the diameter of intact ins correlates with rupture pressures *in vitro*. Proximal phenous segments are of significantly greater diameter than stal segments, and so carry a diminished risk of rupture when ed for carotid patch angioplasty[9]. Furthermore, blowout is ost likely to occur where circumferential wall stress is eatest[9], i.e. the central portion of the vein patch; some thors[4,6] accordingly advocate a maximum safe vein-patch dth of 4–5 mm.

Reluctance to use thigh saphenous vein so as to preserve for future vascular or cardiac surgery has been discounted de Vries *et al.*[13], who demonstrated that less than 15 per cent patients undergoing carotid surgery at their institution quired a secondary vascular procedure within 5 years, and at saphenous vein harvesting from the thigh rarely mpromised subsequent revascularization procedures. Every fort should be made to minimize the complications of carotid darterectomy if it is to remain a worthwhile operation. In ew of the apparent national trend towards patching, it is portant that surgeons who favour arteriotomy closure by eans of vein-patch angioplasty should be alert to the tentially avoidable complication of vein rupture. This applies rticularly in women, who are known to be at increased risk of carotid restenosis[14] and in whom patch angioplasty closure has been shown to be especially beneficial[7]. Avoidance of poor-quality ankle vein and large-diameter patches, and careful perioperative control of blood pressure, should ensure that the risk of patch rupture is minimized.

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Intraoperative measurement of vascular graft resistance as a predictor of early outcome

The quality of distal run-off is one of the most important facto influencing the early outcome of femorodistal vein grafting. Duri femoropopliteal and infrapopliteal bypass, assessment of graft resistan and flow were made using a combination of Doppler flowmeter recordin and measurements of arterial pressure. In a series of 100 reconstructio there were 12 early failures. The mean (95 per cent confidence interv (c.i.)) maximal flow measurement in the group of grafts that fail when anastomosed to the popliteal artery or tibioperoneal trunk w 125 (74–176) ml/min compared with 256 (223–289) ml/min successful grafts ($P = 0{\cdot}006$). *The corresponding figures for graf inserted into a single crural vessel were 99 (72–126) and 16 (137–193) ml/min* ($P < 0{\cdot}02$). *In the group that failed the mea (95 per cent c.i.) resistance after papaverine injection was 1·0 (0·82–1·22) peripheral resistance units (p.r.u.) compared with 0·4 (0·44–0·51) p.r.u. in the successful group* ($P < 0{\cdot}001$). *Using combination of resistance >0·9 p.r.u. and capacity loss ratio aft papaverine injection <10 per cent to identify grafts that subsequent failed, the sensitivity, specificity, positive predictive value, negati predictive value and accuracy were 92, 97, 85, 99 and 97 per ce respectively. These results confirm that haemodynamic measuremen can be used at operation to identify a group of patients in whom bypas is likely to fail.*

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Adequate inflow and outflow (run-off) and a suitable conduit are essential for successful arterial reconstruction. However, failures still occur despite the use of various preoperative methods to evaluate distal run-off[1]. Ascer *et al.*[2–4] and Beard and colleagues[5] have shown that intraoperative measurement of distal resistance is predictive of the outcome of femorodistal bypass. Scott *et al.*[6] showed that intraoperative assessments of resistance correlate with preoperative pulse-generated run-off measurements of the distal outflow. Intraoperative assessment of suitability and a vein conduit for bypass is made on size and possibly on the potential of the vein to dilate[7,8] but little attention has been directed towards its functional capacity. In this study, graft flow and resistance plus a haemodynamic method of measuring vein graft capacity have been used to try to identify grafts that are at increased risk of early failure.

Patients and methods

Between November 1990 and February 1992, 96 patients (65 men, 31 women) of mean age 64 (range 42–91) years who underwent 100 vein bypassses to the popliteal and calf vessels were studied. Twenty-five patients were diabetic. A total of 79 limbs were treated for critical ischaemia, 15 for severe claudication and six for popliteal aneurysm. The site of distal anastomosis was: the proximal popliteal artery (13 grafts), distal popliteal artery or tibioperoneal trunk (44), anterior tibial artery (18), posterior tibial artery (19) and peroneal artery (six).

All patients underwent preoperative intra-arterial digital subtraction arteriography and assessment of distal run-off using Doppler ultrasonography in combination with pulse-generated run-off measurement. A Doppler flowmeter (OPDOP 130; Scimed, Bristol, UK) with an 8-MHz probe was used to assess the capacity of the vein graft by making flow measurements (*Figure 1*) before insertion of the distal anastomosis (Q_1) and after completion of this anastomosis following the administration of 30 mg papaverine hydrochloride (Q_2). T capacity loss ratio after injection of papaverine (CLR_p) was calculat as a percentage using:

$$CLR_p = \frac{Q_1 - Q_2}{Q_1} \times 100$$

Flow measurements open to the atmosphere were also used to he ascertain the success of valve lysis and to aid in correct alignment the graft[9]. Intra-arterial pressure was measured by a transducer to allo resistance to be calculated. Resistance before and after papaveri injection was recorded. Papaverine was administered through a 6- umbilical catheter inserted into the vein graft via a side branc Intra-arterial blood pressure monitoring was performed in all patient Of the 100 grafts, 92 underwent completion arteriography. Haem dynamic measurements were repeated at completion and we correlated with outcome. Failure by 1 month after operation was judge

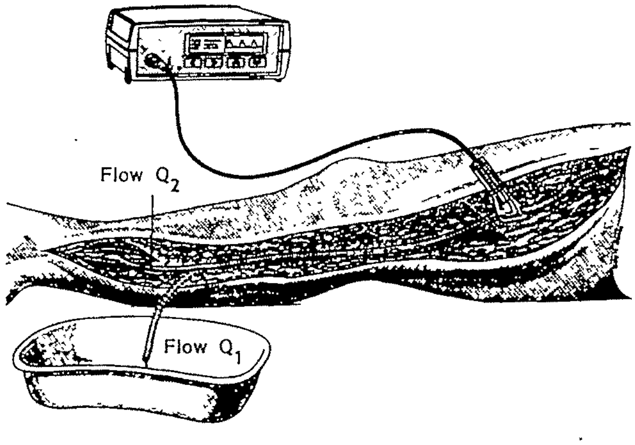

Figure 1 *Schematic representation of flowmeter and the calculation flow (for details see text)*

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iave occurred from the results of angiography, duplex scanning and le:brachial pressure measurement. Systemic heparinization was d during surgery and after operation enteric coated aspirin 0 mg/day) was prescribed.

Statistical analysis was performed using the Mann–Whitney *U* and tests.

sults

ere were 12 failures within 30 days (*Table 1*). Seven occurred grafts anastomosed to a crural vessel, four in grafts istomosed to the distal popliteal artery or tibioperoneal ink and one in a graft anastomosed to the proximal popliteal ery. The 1-month patency rate for pulse-generated run-off f vessel scores ⩽3 and >3 were 84 and 95 per cent pectively.

w measurement

e mean (95 per cent confidence interval (c.i.)) flow asurement open to the atmosphere (Q_1) was 310 16–364) ml/min; there was no significant difference between ups with success and failure. In cases where flow was initially or (<150 ml/min), valve lysis was carried out a second time fore performing the distal anastomosis. The mean (95 per cent .) maximal flow after implantation (Q_2) in the 52 successful ifts to the popliteal artery or tibioperoneal trunk was 256 23–289) ml/min compared with 125 (74–176) ml/min in the e grafts that failed ($P = 0{\cdot}006$). For calf vessels, the mean 5 per cent c.i.) maximal flow in the 36 successful grafts was 5 (137–193) ml/min compared with 99 (72–126) ml/min in seven grafts that failed ($P < 0{\cdot}02$). Flow in successful grafts the popliteal artery or tibioperoneal trunk was significantly eater than that in those to a single crural vessel ($P < 0{\cdot}001$).

sistance

the group that failed the mean (95 per cent c.i.) resting sistance was 1·55 (1·23–1·87) peripheral resistance units .r.u.) compared with 0·78 (0·70–0·86) p.r.u. in the successful oup ($P < 0{\cdot}001$) (*Figure 2*). The corresponding values if paverine was used were 1·02 (0·82–1·22) p.r.u. and 0·47 ·44–0·51) p.r.u. ($P < 0{\cdot}001$) (*Figure 3*). In the successful afts anastomosed to the popliteal artery or tibioperoneal ınk, the mean (95 per cent c.i.) resistance after papaverine ıs 0·40 (0·36–0·44) p.r.u. compared with 0·97 (0·87–1·07) r.u. in those that failed ($P < 0{\cdot}001$). In the successful grafts astomosed to a single crural vessel the resistance after paverine was 0·58 (0·52–0·64) p.r.u. compared with 1·09 ·65–1·43) p.r.u. in those that failed ($P = 0{\cdot}003$). In the 52 ccessful grafts anastomosed to the popliteal artery or ioperoneal trunk, the resistance after papaverine was significantly less than that in those anastomosed to a calf vessel ($P < 0{\cdot}001$). Three grafts had a resistance >1·5 p.r.u. after papaverine injection following completion arteriography. These were immediately revised as an easily correctable problem was identified. A distal jump graft was performed in two and vein patch angioplasty of a stenosis at the origin of the anterior tibial artery carried out in the third.

All three patients in whom grafting failed who had a measured resistance after papaverine injection of <0·9 p.r.u. suffered failure from a technical problem with the conduit (one retained valve, one poor vein segment, one graft inserted under

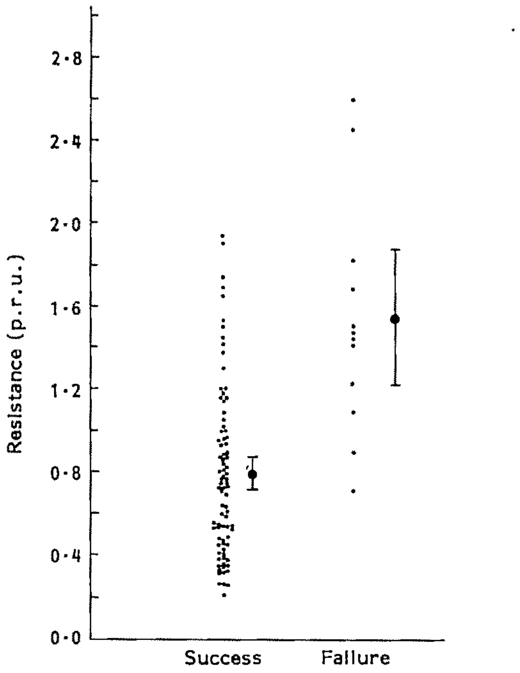

Figure 2 *Relationship between resting resistance measured in peripheral resistance units (p.r.u.) and graft outcome. Bars are mean (95 per cent confidence interval).* $P < 0{\cdot}001$ *(Mann–Whitney* U *test)*

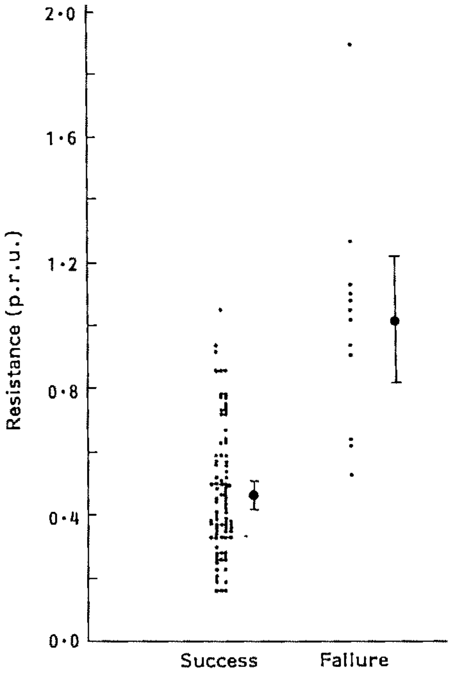

Figure 3 *Relationship between resistance after injection of papaverine measured in peripheral resistance units (p.r.u.) and graft outcome. Bars are mean (95 per cent confidence interval).* $P < 0{\cdot}001$ *(Mann–Whitney* U test)

ble 1 *Cause of graft failure and outcome in 12 patients*

itient).	Cause of failure	Procedure	Patent	Limb salvage
iastomosis to popliteal artery tibioperoneal trunk				
1	Run-off	Amputation	No	No
2	Vein conduit	Revision	Yes	Yes
3	Run-off	Revision (twice)	No	No
4	Vein conduit	Revision	Yes	Yes
5	Run-off	Revision	No	Yes*
iastomosis to calf vessels				
6	Run-off	Revision (twice)	Yes	Yes
7	Run-off	Revision (3 times)	No	No
8	Run-off	Amputation	No	No
9	Run-off	Amputation	No	No
10	Run-off	Revision	No	No
11	Run-off	Revision	No	No
12	Vein conduit	Revision	Yes	Yes

*Performed for claudication

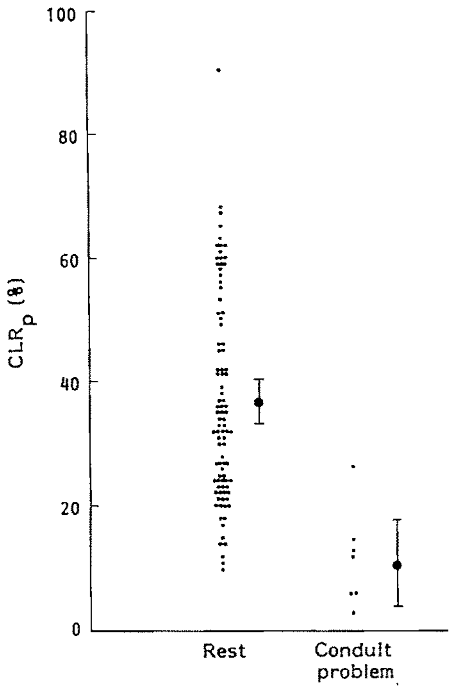

Figure 4 *Relationship between vein capacity loss ratio after injection of papaverine (CLR_p) and conduit problems. Bars are mean (95 per cent confidence interval).* $P < 0{\cdot}001$ *(Mann–Whitney* U *test)*

Table 2 *Predictive value with respect to graft failure of resistance measurements after papaverine injection*

	Resistance >1 p.r.u.	Resistance >0·9 p.r.u.	Resistance >0·9 p.r.u. and CLR$_p$ <10%
Sensitivity	58	75	92
Specificity	99	97	97
Positive predictive value	88	75	85
Negative predictive value	95	97	99
Accuracy	94	94	97

Values are percentages. p.r.u., Peripheral resistance unit; CLR$_p$, capacity loss ratio after papaverine injection

tension which caused marked narrowing). Following revision the resistances after papaverine were $<0{\cdot}6$ p.r.u. and the grafts were patent at 30 days. Four other patients (one with a poor vein segment, one with a retained valve cusp, two with an arteriovenous fistula) who required graft revision during the first week after surgery also had a low capacity loss ratio after papaverine injection. This ratio in vein grafts that failed or were deemed at risk because of a conduit problem was significantly lower than that in the remainder ($P < 0{\cdot}001$) (*Figure 4*). *Table 2* shows the overall predictive value of resistance measurement and capacity loss ratio in terms of subsequent outcome.

Outcome

In total, 16 grafts required one or more reoperations. Of the 12 patients with failed grafts, three underwent early amputation as further reconstruction was not possible because of inadequate run-off. Five failed grafts were successfully revised: thrombectomy and valve lysis (one); thrombectomy and interposition graft (two); thrombectomy and revision of distal anastomosis (one); and thrombectomy and distal jump graft (one). Four grafts were revised but subsequently failed: thrombectomy and replacement with contralateral long saphenous vein (one); thrombectomy alone (two); and thrombectomy and vein patch at the distal anastomosis (one). Thirteen reoperations were required in 43 grafts anastomosed to a crural vessel compared with seven in 57 grafts anastomosed at a more proximal s ($P < 0{\cdot}05$).

Discussion

The possible causes of graft failure are: poor-quality vein, gr trauma, malalignment, persistent valves or tributari anastomotic narrowing, proximal or distal disease, inadequa graft perfusion, hypercoagulability and sepsis. The last tv causes cannot be identified by simple haemodynam measurement taken at the time of operation.

Failure of a bypass distal to the groin has significant clinic and financial implications[10,11] and such failure still occu despite numerous preoperative investigations. Intraoperati investigation may improve quality control and act as a predict of outcome. The simplest intraoperative technique to give indication of distal resistance is the 'feel' of the syringe duri an injection into the distal run-off[12]. Wheale *et al.*[13] suggest that resistance measurement should be made at the time maximal flow and this led to the use of vasoactive drugs lower resistance during measurement[4,5,14,15]. In a previo study the present authors demonstrated that assessment distal resistance using a Doppler flowmeter and pressu measurement allowed prediction of grafts that were likely fail[5]. In this earlier study, the measurement of resistance aft a vasodilator was particularly sensitive in predicting outcom In the present series, however, the difference between t predictive value of resistance measurements with and witho vasodilator was less marked. This could be explained by a increased number both of patients with severe ischaemia an of crural grafts. In view of the previous results[5], it w considered unethical not to intervene in three patients, wh had immediate revision. The measurements after revision we included in the present analysis.

Intraoperative assessment of vein is often made by visu inspection of size and preinsertion distension, although th latter technique may be responsible for endothelial damage Angioscopy in the preparation of the vein may eventuall become routine and this may help achieve the optim conduit[16–19]; angioscopy was not available during the prese study. Measurement of the capacity loss ratio after papaveri injection in the present series appears to have been useful. low ratio may be associated with a graft at risk of failu secondary to a conduit problem. Its benefit in this group patients has been to increase the sensitivity of th haemodynamic method in predicting early failure. Gra resistance and flow measurements made at the end of th procedure do not identify problems until the distal anastomos is complete. They can, however, successfully identify grafts th are likely to benefit from revision. In some patients in who haemodynamic measurements suggest that failure is likely t occur and for whom no corrective procedure is possible, decision to perform early amputation may be made and fruitles re-exploration avoided.

Acknowledgements

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Announcement

The Vascular Surgical Society of Great Britain and Ireland

The Annual General Meeting of the VSS this year will be held at the Royal Northern College of Music in Manchester on 18 and 19 November. Following receipt of a generous offer of sponsorship by The British Journal of Surgery Society, Council has decided that two separate prizes will be awarded for papers presented at the AGM.

The British Journal of Surgery Prize will be awarded for the best paper presented by a surgeon in training on basic or laboratory-based vascular research. The Founder's Prize will be awarded for the best paper presented by a surgeon in training on clinical research. The value of each prize is £500.

Further information about eligibility and instructions for entering will be circulated with the abstract and registration documents for the meeting.

P. L. Harris
Secretary
Vascular Surgical Society
of Great Britain and Ireland

Surgical workshop

Br. J. Surg. 1993, Vol. 80, July, 858–859

Intraoperative thrombolysis in the management of thrombosed popliteal aneurysm

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Thrombosis of a popliteal aneurysm is a disaster with a higher amputation rate than all other causes of acute lower-limb ischaemia. The treatment of choice is bypass grafting, but results are often poor because of acute distal thrombosis or chronic distal embolization[1].

Intra-arterial thrombolysis is effective for selected patients with thrombosed popliteal aneurysm[2]. However, those with severe acute critical ischaemia including a neurological deficit from a poor collateral supply cannot wait for thrombolysis to work; urgent surgery is required. Intraoperative thrombolysis, which has been undertaken to lyse residual clot after balloon embolectomy[3], has been used in this situation.

Surgical technique

Six patients presented with acute lower-limb ischaemia and underwent arteriography, which confirmed the diagnosis of thrombosed popliteal aneurysm. Thrombolysis was started in two patients with viable limbs, but deterioration prompted intervention before the clot could be lysed. Four patients with severe ischaemia required urgent surgery.

Under general anaesthesia, the popliteal artery was exposed by an anteromedial approach and the aneurysm ligated. Balloon embolectomy of the tibial vessels was performed. On-table arteriography was carri out using 20 ml non-ionic contrast agent and intraoperative ly performed if residual thrombus was seen (*Figure 1*). Streptokinase tissue plasminogen activator was made up to a volume of 50 ml wi saline and infused over 30 min using a syringe driver set at 99·9 ml/ A combined embolectomy–irrigation catheter (Meadox UK, Caddin ton, UK) was found to be convenient for embolectomy, lysis a arteriography. Meanwhile, construction of the proximal anastomo of the reconstruction proceeded.

Results

Six consecutive patients were treated (*Table 1*). This represen the total experience with this approach: there were r exclusions. All had functioning grafts, confirmed by angiograp and non-invasive studies, and all had the limb saved. T minimum follow-up was 6 months. There were no complicatio related to lysis. Low-dose intra-arterial thrombolysis is n associated with systemic effects, so no haematologic monitoring was performed. In particular there was no excessi bleeding after fasciotomy.

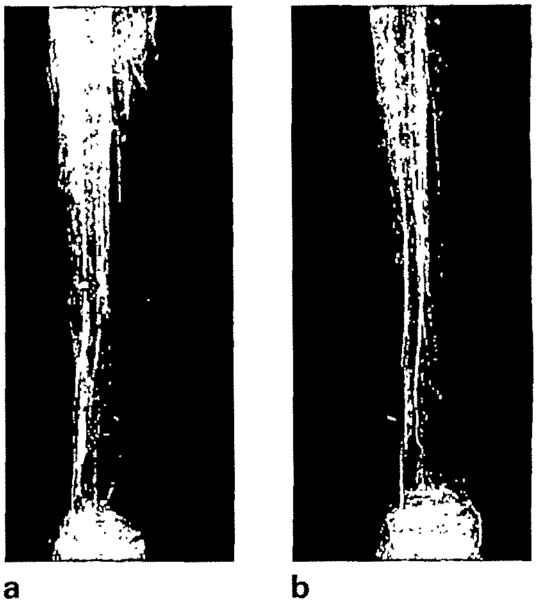

Figure 1 *Intraoperative angiograms showing* **a** *residual thrombus i crural arteries after embolectomy (arrows).* **b** *Run-off is improve following thrombolysis*

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Table 1 *Results of intraoperative thrombolysis*

Patient no.	Sex	Age (years)	Lysis method	Operation	Peroperative angiography	Additional procedures	Outcome
1	M	56	100 000 units streptokinase	PTFE graft (vein cuff)	Confirmed lysis	Fasciotomies Skin grafts	DSA satisfactory ABPI > 1·0 Duplex scan normal
2	M	54	3·0 mg tPA	*In situ* vein graft	Confirmed lysis	Fasciotomies Skin grafts	DSA satisfactory ABPI 0·85 Duplex scan normal
3	M	69	1·0 mg tPA	*In situ* vein graft	Not performed	Vein patch at proximal anastomosis	DSA satisfactory
4	M	73	100 000 units streptokinase	PTFE inlay graft	Confirmed lysis	None	Atheroembolus ABPI 0·61
5	M	57	100 000 units streptokinase	Reversed vein graft	Confirmed lysis	Fasciotomies; closed under local anaesthesia	DSA satisfactory ABPI 1·0
6	M	77	100 000 units streptokinase	*In situ* vein graft	Confirmed lysis	None	DSA satisfactory ABPI 0·91

tPA, tissue plasminogen activator; PTFE, polytetrafluoroethylene; DSA, digital subtraction angiogram; ABPI, ankle: brachial systolic pressure index

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iscussion

:ute thrombosis of a popliteal aneurysm is, fortunately, rare. ten the most constructive option is to bypass a contralateral eurysm, if present. Prevention of the thrombosis of a popliteal eurysm by elective surgery requires early detection, which y be possible in those with aneurysms elsewhere. However, re is a morbidity associated with operations on asymptomatic tbs[4]. As thrombolysis has been shown to be effective for pliteal aneurysm thrombosis, a less aggressive surgical stance justified: patients with subcritical ischaemia may have low se intra-arterial thrombolysis to clear the run-off before onstruction. However, the radiological expertise required to nage intra-arterial thrombolysis is not always available or ne may be limited by severe ischaemia; in this situation raoperative thrombolysis brings advantages of simplicity and ety.

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hort note

. J. Surg. 1993, Vol. 80, July, 859

utureless circumcision

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ircumcision is a common surgical procedure in which mucosa id skin apposition is usually achieved with interrupted catgut itures. Newer techniques of skin closure have recently been ported[1]. Early experience using the tissue adhesive -butyl-2-cyanoacrylate monomer (Histacryl; Davis and eck, Gosport, UK) to approximate mucosa and skin after ective circumcision is presented.

atients and methods

xty consecutive patients of median age 5·3 (range 1–64) years were udied. Indications for circumcision were phimosis (43 patients), current balanoposthitis (12) and religious or social (five).

Ethical committee approval was obtained before starting the study. ll patients, or parents of minors, gave informed consent.

After excision of the foreskin, careful haemostasis was obtained by gation of blood vessels. Mucocutaneous approximation was achieved ing toothed forceps and Histacryl, which was applied in a thin layer ound the edges. These were held together for at least 10 s. After lherence of the mucocutaneous junction, an adhesive permeable astic dressing (Opsite; Smith and Nephew Medical, Hull, UK) was applied. All individuals were reviewed as outpatients 2 weeks after surgery.

Results

Good skin approximation with circumferential adherence of the mucocutaneous junction was always obtained within 2 min of applying Histacryl. The cosmetic appearance at 2 weeks was excellent in all cases. There was no incidence of wound breakdown although one patient had a wound infection that resolved on antibiotics. The clinical impression was of reduced scar formation without stitch holes compared with conventional mucocutaneous apposition. No adverse reactions to Histacryl were reported and no remaining adhesive was detected at 2 weeks. All participating surgeons reported Histacryl to be easy to use and quicker than conventional suturing.

Discussion

The use of Histacryl to obtain mucocutaneous apposition after circumcision appears to avoid the complications that may result from conventional suturing such as a poor cosmetic result from suture tracks, poor tissue approximation, an apparently longer operating time and the discomfort of sutures that may adhere to or snag clothing and dressings. The adhesive was technically easier to use and faster than conventional suturing. Costs were comparable to those of the conventional procedure, taking these factors into account.

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Non-therapeutic operations for penetrating trauma: early morbidity and mortality

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A prospective study was carried out to assess the incidence and type complications after non-therapeutic operations for penetrating traum A total of 372 operations were performed on 368 patients wi penetrating injuries to the abdomen (240 procedures), chest (49), ne (48) and extremities (35). There were 46 negative or non-therapeut operations. The incidence of major complications directly related anaesthesia or operation in this group of patients was 4 per cent (tw patients). The operation might have contributed to a further three maj complications. The mean hospital stay for patients undergoi uncomplicated non-therapeutic operation was 4·1 days; for those wi complications it was 21·2 days. It is concluded that non-therapeut operations for penetrating trauma carry a significant morbidity rate. policy of selective conservatism is advocated.

The indications for surgical exploration in penetrating trauma vary significantly in various trauma centres and many controversial issues remain unresolved. Many centres apply some form of selective conservatism, using a variety of diagnostic criteria ranging from clinical examination alone to major invasive investigations. Other centres advocate a policy of liberal surgical exploration, claiming that non-therapeutic operations carry neither mortality nor significant morbidity. However, very few studies have investigated the risks of non-therapeutic operations for trauma. With this in mind a prospective study was conducted to assess the incidence and nature of complications in non-therapeutic operations.

Patients and methods

This was a prospective study performed at Baragwanath Hospital by two of five trauma teams over a period of 13 months between January 1991 and February 1992. The study group included all patients operated on for penetrating trauma. An operation was considered to be non-therapeutic if there was no significant organ injury requiring repair, i.e. non-bleeding solid organ wounds, haematoma and serosal laceration of hollow viscera. Final analysis was performed only in the group of patients undergoing non-therapeutic operation. These patients were monitored closely for early postoperative complications. Pneumonia was diagnosed if there was either fever or coughing of purulent sputum, and an infiltrate on the chest radiograph. An incision wound was considered to be infected if there was pus or severe erythema requiring removal of sutures or administration of antibiotics. Minor erythema around the wound or non-purulent discharge that was bacteriologically sterile was not included.

All patients scheduled for operation received antibiotic prophylaxis with a cephalosporin before surgery. The antibiotic was discontinued after operation if the procedure was non-therapeutic. Closed drains were used depending on the judgement of the operating surgeon.

Results

During the study period, 368 patients were subjected to 372 operations. Knife injuries accounted for 70·1 per cent and gunshot wounds for 29·9 per cent of cases. The mean age of the patients was 26 years and 95·1 per cent were male. The commonest operation was laparotomy (240 procedures), followed by thoracotomy (49), neck exploration (48) and exploration of an extremity (35).

Overall, 46 non-therapeutic procedures (12·4 per cent) were performed. There was no difference in the incidence of non-therapeutic exploration between knife and gunshot injuries (13 *versus* 12 per cent). The regions of the body operated on and the respective incidence of non-therapeutic procedures ar complications are shown in *Table 1*. Findings in the 4 unnecessary operations were: 21 cases of minor bleeding (bleeding that had stopped by the time of operation, eig haematomas, 11 parenchymal injuries not requiring repai three eviscerations from abdominal stab wounds, two cases pericardial penetration without underlying cardiac injury an 14 completely negative operations (a negative exploration ra of 3·8 per cent). Three of the negative procedures we performed in patients with associated spinal cord injury.

Table 1 *Operations for penetrating trauma*

		Non-therapeutic operations	
Body area	No. of operations	No. performed	No. of complicatio
Abdomen	240	35	4
Chest	49	5	1
Neck	48	6	0
Extremities	35	0	0
Total	372	46	5

In the group of patients receiving 46 non-therapeut operations there were five major complications (11 per cen (*Table 2*). Two complications were directly related to t operation (patients 2 and 3). A further three patients develop complications possibly related to the operation (patients 1, and 5). The mean hospital stay for all non-therapeut operations (excluding patients with associated spinal injurie was 5·8 days. The mean hospital stay for patients with a uncomplicated postoperative course was 4·1 days and for tho with major complications 21·2 days.

Discussion

The role of non-operative management in penetrating injury much debated. Many authors support mandatory operati for all neck injuries that have violated the platysma. Similar liberal or even mandatory surgical intervention in penetrati trauma of the chest or abdomen has been advocated in ma studies[1–4]. Proponents of such a policy believe that physic examination is not reliable in detecting significant injury a that when there is doubt operative exploration is better. Th

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ble 2 *Major morbidity in non-therapeutic operations*

tient	Age (years)	Operation	Associated injuries	Operative findings	Complications	Hospital stay (days)
	24	Thoracotomy	None	Hole in pericardium Haemopneumothorax	Pancreatitis	12
	30	Laparotomy	None	Haematoma	Aspiration pneumonia Wound sepsis Perioral herpes	31
	65	Laparotomy	None	Negative	Wound sepsis	19
	16	Laparotomy	Haemopneumothorax	Negative	Deep vein thrombosis	35
	30	Laparotomy	Haemopneumothorax	Negative	Pneumonia	9

im that non-therapeutic operations are safe, with no ortality and only minimal morbidity. However, very few udies support this claim: most have reported a significant orbidity rate and even deaths after non-therapeutic operation. ance *et al.*[5] reported eight serious iatrogenic visceral injuries a series of 250 negative laparotomies. Petersen and Sheldon[6] und a complication rate of 17 per cent (mostly minor mplications) in 94 patients with stab wounds of the abdomen d a negative laparotomy. More recent studies have yielded milar results. Weigelt and Kingman[7] reported a complication te of 37 per cent in 248 patients with a negative laparotomy. Many of these complications occurred in patients with sociated injuries; however, the complication rate in those ith no associated injury was still 22 per cent. Sirinek *et al.*[8] ted a mortality rate of 0·2 per cent and a morbidity rate of per cent for negative laparotomy. In the present study the cidence of severe complications directly related to anaesthesia the operation was 4 per cent. A further 7 per cent of patients d complications possibly related to the operation. It must stressed that these are results from a large academic hospital ith extensive experience in trauma.

It should not be surprising that significant complications llow non-therapeutic operation. These are emergency ocedures on unprepared patients who often have a full omach and alcohol intoxication. They are also often rformed in the middle of the night, perhaps by relatively nior staff.

We believe that a policy of selective conservative anagement can safely be applied to most patients with enetrating trauma. It has been shown that 85 per cent of enetrating injuries of the chest[9], about 45 per cent of stab ounds of the anterior abdomen[10], 85 per cent of penetrating juries of the back[11] and 25 per cent of bullet wounds of the bdomen[12] can be managed safely without operation. ndications for surgical intervention in the present authors' unit have been described previously[9–12] and are not discussed in this article.

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Electrocautery of the upper thoracic sympathetic chain: a simplified technique

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Several techniques for endoscopic ablation of the upper thoracic chain have been described[1–5]. As these gain popularity, especially in the treatment of hyperhidrosis, a new procedure used on 450 patients is reported that is much simpler than previous techniques. A standard single-lumen endotracheal tube and anterior approach obviate the need for abduction and suspension of the arms[1–5] and permit a bilateral procedure without repositioning of the patient. Because standard urological electrocautery equipment is used, there is no need for a second incision[1,2] to introduce a diathermy probe. The nerves are treated with diathermy and no attempt is made to extirpate the ganglia with a forceps[4,5]. Only the second and third thoracic ganglia are coagulated and divided for treatment of palmar hyperhidrosis.

Surgical technique

The operation is performed under general anaesthesia with the patient positioned half sitting; hypotension is controlled with dihydroergotamine (0·25–0·5 mg intravenously). The intercostal space between the first and second ribs is incised approximately 2 cm below the clavicle and 2 cm lateral to the sternum and a Verres needle introduced into the pleural cavity. An apical pneumothorax is created by insufflation of 2 litres carbon dioxide. The needle is changed to a modified (piercing-point) 7-mm urological cannula through which the electroresectoscope is introduced (*Figure 1*). The sympathetic chain is usually seen through the parietal pleura passing over the ribs close to the costovertebral junction. The nerve is sometimes obscured by overlying subpleural fat but can then be identified by 'palpation' with the resectoscope sling. The sympathetic chain overlying the second and third ribs is treated with diathermy down to the periosteum. The intercostal space harbouring somatic nerves and blood vessels is left untouched. The nerve of Kuntz (a branch parallel and lateral to the main trunk) is present in around 10 per cent of patients and must be coagulated. Failure to destroy this nerve may lead to incomplete denervation of the upper extremity. By leaving the first rib with the lower part of the stellate ganglion untouched the risk of Horner's syndrome is minimized. If axillary hyperhidrosis is a prominent symptom, the fourth thoracic segment should be treated. Before closure of the wound, the lung is expanded by positive end-expiratory pressure combined with suction through a small catheter.

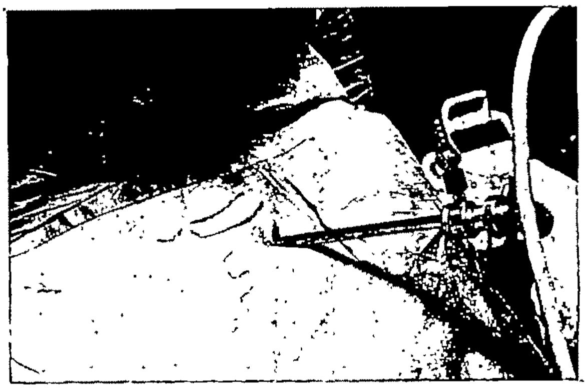

Figure 1 *Endoscopic treatment of palmar hyperhidrosis. The pleu cavity is entered in the mid-clavicular line 2 cm below the clavicle. T second and third thoracic segments of the sympathetic chain are destro by electrocautery with a standard urological electroresectoscope*

Chest radiography is performed a few hours after operation. A remaining 15–30-mm wide apical carbon dioxide pneumothorax quickly absorbed and requires no further therapy or check.

Results

The median operating time for a bilateral procedure is 25 mi patients are routinely discharged after an overnight stay ar resume work within 1 week. Complications have bee comparatively few and minor: three patients with pneumothorax and one with a haemothorax required suctio drainage; and one Horner's syndrome occurred when the low part of the stellate ganglion was included in the procedure. C a total of 900 procedures during 1987–1992, there were eig failures and four patients with early recurrence. Despite pleur adhesions, reoperations were successful. In two patient adhesions prevented sympathectomy; the patients ha previously been operated on by open sympathectomy. Th simplified technique using standard hospital equipment ha been shown to be efficient, fast and safe.

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Screening for breast cancer detects tumours at an earlier biological stage

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Between August 1988 and July 1990, 17 678 women in the Gateshead, Sunderland, South Tyneside and Durham districts attended the national breast screening programme. A total of 131 cancers were detected. The morphology of cancers detected by screening was compared with that of tumours in 71 patients presenting clinically in the same period. Screen-detected cancers included a higher proportion of tumours of more favourable histological grade and type, were smaller in size and had less axillary lymph node involvement than those detected clinically. Survival was predicted from the Nottingham Prognostic Index. Patients with screen-detected cancer had an expected survival advantage (95 per cent confidence interval) of 26·5 (12·3–40·6) per cent at 5 years, 26·5 (11·8–41·2) per cent at 10 years and 29·1 (14·5–43·7) per cent at 15 years. This survival advantage in screened patients expected at 5, 10 and 15 years is consistent with the 30 per cent reduction in mortality rate demonstrated in the Health Insurance Plan study and the Swedish two counties trial.

A national breast screening programme was started in the UK in August 1988 following the recommendations of the Forrest eport[1]. On the evidence of two trials[2,3] the report concluded hat the mortality rate from breast cancer in Britain in the 50–64 years age group could be reduced by 30 per cent. Data published by the UK Trial of Early Detection of Breast Cancer Group[4] showed a 14 per cent reduction in mortality rate at 7 years but this was not statistically significant. The results were claimed to be consistent with a reduction in mortality rate of 30 per cent.

Fundamental to the achievement of a reduction in mortality ate is the demonstration of a biological difference between creen-detected cancers and those presenting clinically. In this study the morphological differences between cancers detected through the breast screening programme and those presenting clinically were compared. Survival was predicted from the Nottingham Prognostic Index (NPI), which has now been validated[5] to 15 years.

Patients and methods

Between August 1988 and July 1990, 25 815 women in the Gateshead, Sunderland, South Tyneside and Durham districts were invited as part of the prevalent breast screening programme. In all, 17 678 attended (compliance rate 68·5 per cent) and underwent single-view mammography. A total of 131 cancers in 129 women were detected, a rate of 7·4 per 1000 women screened. There were 64 impalpable lesions requiring guidewire localization biopsy and 67 palpable tumours. These were compared with 71 cancers presenting clinically during the same period.

All patients were treated by two consultant surgeons using the following strategy. With a lesion $\leqslant 3$ cm in size, if preoperative fine-needle cytology confirmed cancer, patients were offered a choice of segmental mastectomy, axillary node dissection and postoperative radiotherapy to the breast (breast conservation), or simple mastectomy and axillary node dissection. Excision biopsy was undertaken if cytology was not indicative of cancer or not performed, and patients subsequently offered the above choice. Patients with ductal carcinoma *in situ* (DCIS) but without evidence of microinvasion required no further surgery if adequate resection margins were shown histologically. These patients were not given radiotherapy. Patients with DCIS and microinvasion were offered breast conservation and radiotherapy or mastectomy. Those with cancers >3 cm in diameter were advised to accept simple mastectomy and axillary node dissection.

Axillary lymph node dissection included all nodes in levels I and II. Although sampling of nodes in level I has been reported to be as accurate as total axillary clearance[6], dissection of levels I and II of the axilla has been advocated for improved prognosis and prophylaxis against local recurrence[7]. The histological status of nodes in level II was required for assessment of the NPI. Radiotherapy to the axilla was given if more than three nodes in level I or any node in level II showed metastatic spread of tumour.

After surgical excision, specimen radiographs were taken of screen-detected cancers to confirm removal of the radiological lesion. Tumour size was measured in the fresh specimen but, if subsequent histological sections demonstrated a discrepancy, the maximum dimension measured on the section was accepted. A grading score was applied to all invasive tumours using Elston's modification of the Bloom and Richardson system[8]. Microinvasion in DCIS was defined as one or more foci of definite stromal infiltration measuring $\leqslant 1$ mm and occurring in a tumour otherwise *in situ*.

The NPI was calculated from tumour size, grading of lesion and lymph node status[9]. Prognosis was categorized as good (NPI $<3·4$), moderate (NPI 3·4–5·4) or poor (NPI $>5·4$). Survival in each of these patient groups has been validated[5] to 15 years. The survival rate in screened and clinical patients was predicted according to the distribution within the NPI categories and compared with that of an age-matched control group without breast cancer. The survival rate in this group was derived from mortality statistics issued by the Office of Population Censuses and Surveys[10] (M. H. Galea and J. L. Haybittle, personal communication). The predicted survival advantage and 95 per cent confidence intervals were calculated (Confidence Interval Analysis program; British Medical Association, London, UK). χ^2 analysis was used to test for differences in predicted survival and the incidence of various histological parameters between screen-detected and clinically presenting cancers. $P < 0·05$ was considered significant.

Results

Tumour histology (Table 1)

Invasive ductal cancers not otherwise specified comprised 90 per cent ($n = 64$) of clinical tumours, and 82 per cent ($n = 55$) of palpable and 48 per cent ($n = 31$) of impalpable screened lesions. There were significantly more invasive tumours of specialized type in the screen-detected population ($\chi^2 = 4·12$, 1 d.f., $P = 0·04$). Screen-detected cancers not otherwise specified had a better histological differentiation compared with clinical tumours ($\chi^2 = 6·67$, 2 d.f., $P = 0·04$).

Vascular invasion was present in 17 per cent ($n = 12$) of clinical cases and 6 per cent ($n = 4$) of screened palpable lesions but in no patient with an impalpable tumour. Nerve sheath invasion was present in 35 per cent ($n = 25$), 21 per cent

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Table 1 *Tumours by histological type*

	Screened		
	Impalpable	Palpable	Clinical
Not otherwise specified			
I	12	17	19
II	17	24	22
III	2	13	23
Unspecified	0	1	0
Tubular	6	2	0
Medullary	2	1	2
Lobular	1	4	1
Mucinous	0	3	2
DCIS	21	1	2
DCIS plus microinvasion	3	1	0
Total	64	67	71

DCIS, ductal carcinoma *in situ*

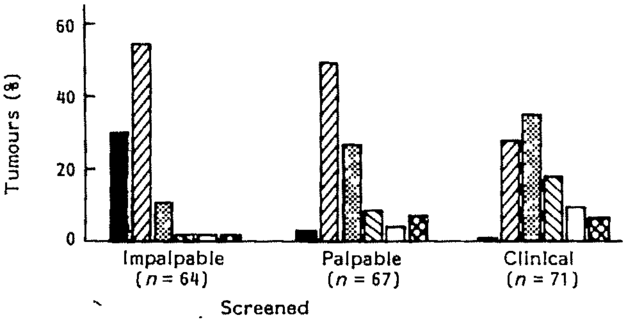

Figure 1 *Tumour size.* ■, *<1·0 cm;* ■, *1·0–1·9 cm;* ▨, *2·0–2·9 cm;* ■, *3·0–3·9 cm;* □, *4·0–4·9 cm;* ▩, *≥5·0 cm*

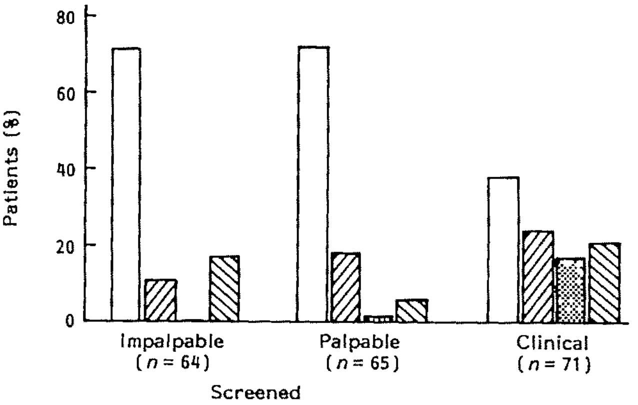

Figure 2 *Lymph node involvement.* □, *No nodes;* ■, *one to three nodes;* ▨, *four or more nodes;* ■, *not sampled*

($n = 14$) and 5 per cent ($n = 3$) of the groups respectively. Vascular ($\chi^2 = 9{\cdot}20$, 1 d.f., $P < 0{\cdot}005$) and nerve sheath ($\chi^2 = 9{\cdot}13$, 1 d.f., $P < 0{\cdot}005$) invasion were significantly more common within invasive tumours presenting clinically than in those detected by screening.

DCIS was found in 3 per cent ($n = 2$) of clinical, 3 per cent ($n = 2$) of screened palpable and 38 per cent ($n = 24$) of screened impalpable tumours. Three of 24 cases of DCIS in impalpable tumours showed microinvasion. DCIS was significantly more common in screen-detected cancers ($\chi^2 = 23{\cdot}82$, 1 d.f., $P < 0{\cdot}005$).

Tumour size (Figure 1)

As expected there was a higher proportion of smaller tumours in the screened group and relatively more large lesions in those presenting clinically.

Lymph node involvement (Figure 2)

Some 86 per cent of all patients underwent axillary n dissection. The median number of nodes removed was 9 (ran 0–27) and was similar in all three groups. Eleven patien (17 per cent) with screen-detected impalpable tumours did n undergo axillary dissection. Nine of these had no further surge after excision biopsy showed DCIS without microinvasion an adequate resection margins. Two patients were considered un for further surgery.

Eleven patients (15 per cent) with cancers detected clinicall received no axillary dissection and in a further four dissectio was performed but no involved nodes found.

Nottingham Prognostic Index (Figure 3)

The NPI was, by definition, calculated for invasive tumou only. The majority of patients with screened impalpable lesion were in the good prognosis group and none had a poo prognosis. Increasing proportions of patients with screene palpable and clinical cancers had moderate and poor prognose

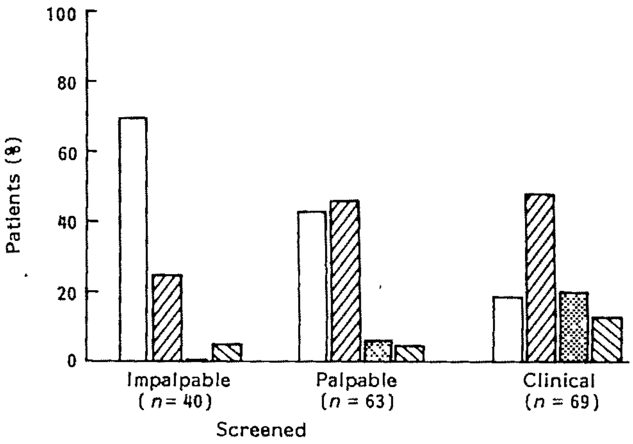

Figure 3 *Nottingham Prognostic Index of patients with invasi tumours.* □, *<3·4;* ■, *3·4–5·4;* ▨, *>5·4;* ■, *not calculated*

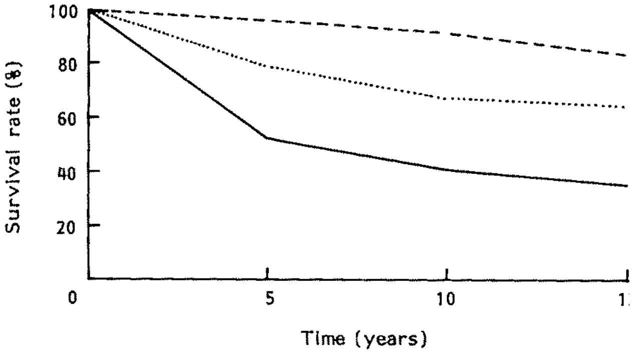

Figure 4 *Expected survival rate.* ——, *Patients with tumours detecte clinically;* ·····, *patients with tumours detected by screening;* – – –, *control*

Table 2 *Survival data for* Figure 4

	Time (years)			
	0	5	10	15
Clinical	71 (100)	37 (52·1)	29 (40·8)	25 (35·
Screened				
Palpable	60 (100)	45 (75·0)	38 (63·3)	35 (58·
Impalpable	38 (100)	32 (84·2)	28 (73·7)	28 (73·
Total	98 (100)	77 (78·6)	66 (67·3)	63 (64·
Controls*	(100)	(96·0)	(91·0)	(83·

Values in parentheses are percentages. *Data from M. H. Galea an J. L. Haybittle, Nottingham *urvival* (Figure 4; Table 2)

pected survival rates at 5, 10 and 15 years were 52·1, 40·8 d 35·2 per cent for patients with tumours presenting clinically d 78·6, 67·3 and 64·3 per cent for those with screen-detected sions. A survival advantage (95 per cent confidence interval) 26·5 (12·3–40·6) per cent at 5 years, 26·5 (11·8–41·2) per cent 10 years and 29·1 (14·5–43·7) per cent at 15 years was edicted for patients with screen-detected tumours. There was significantly greater expected survival rate at 5 years $^2 = 10{\cdot}89$, 1 d.f., $P < 0{\cdot}005$), 10 years ($\chi^2 = 11{\cdot}75$, 1 d.f., $< 0{\cdot}005$) and 15 years ($\chi^2 = 21{\cdot}04$, 1 d.f., $P < 0{\cdot}005$) sociated with screen-detected as opposed to clinically esenting tumours.

iscussion

e endpoint for analysis in screening for breast cancer is ath. A significant reduction in mortality rate was shown in e Health Insurance Plan (HIP) study[2] at 10 years and in the vedish two counties trial[3] at 8 years. It will be some time fore changes in mortality rate are detected in the UK. The ocess may well produce a lead-time bias. Detection of cancers ith more favourable biological characteristics is vital for reening to influence long-term survival rates.

DCIS was present in 19·8 per cent of the present screened ncers, an incidence comparable to those reported in the uildford[11] and Edinburgh[12] series. The presence of DCIS has en found in a high proportion of the affected and contralateral easts of patients with mammary cancer[13]. A synchronous mour was present in only 0·1 per cent of the same breasts d bilateral lesions in 4–10 per cent[14]. Not all DCIS appears progress to invasive cancer but which lesions and what oportion are clinically important are as yet unknown. The cal recurrence rate with invasive cancer when DCIS was eated by local excision alone has been reported[15] to be as igh as 30 per cent at 6 years. DCIS is an important finding d inappropriate treatment may expose these patients to a igh risk of later invasive cancer.

Screened patients in the present study had more tumours f specialized type, which carry a better prognosis than the not therwise specified cancer type. The proportion of tumours of ecialized type in this study was smaller than that in the reened group of patients in a randomized trial reported from dinburgh[16]. In the clinical cancers of not otherwise specified pe there was an even distribution across Bloom and ichardson grading, whereas only two patients with impalpable mours had grade III disease. Vascular and nerve sheath vasion were significantly more common in clinically detected ncers and are associated with a poorer prognosis. No patient ith an impalpable screen-detected tumour had vascular vasion. There was a higher percentage of metastatic lymph odes in clinical as opposed to screen-detected cancers. Tumour rading and lymph node involvement have the largest eterminant value in the NPI, with the size of the tumour (in ntimetres) having only one-fifth of the effect. Screen-detected mours were smaller than those presenting clinically. The size istribution of screen-detected cancers in the present study was mparable to that found by Anderson *et al.*[12].

The differences demonstrated in this comparative study are om a prevalent screened population. Reduction in tumour ze, better histological type and grade, and less lymph node volvement are to be expected from an incident screened opulation. Greater differences between screened and clinically esenting cancers may be seen in the future.

A difference in tumour biology in patients whose cancer was detected by mammographic screening has been demonstrated. This study does not, however, answer the possible significance of lead-time bias or patient selection bias within the screened population. The survival rate at 5 years in patients with screen-detected cancer was predicted to be 78·6 per cent compared with 52·1 per cent for those with clinical lesions. This is consistent with the 30 per cent reduction in mortality rate in the HIP[2] and Swedish two counties[3] studies. Within 5 years of starting breast screening, demonstration of a significant increase in survival within the screened population is expected and it is predicted that this advantage will be maintained at 15 years.

Acknowledgements

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Cytodiagnosis of breast disease using a liquid suspension medium

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Fine-needle aspiration cytology specimens from 187 breast lesions we processed using conventional slide cytology. Results were compared wi those from 201 lesions prepared using a liquid suspension mediu (Cytospin) for specimen collection, to assess the clinical utility of ea technique. The frequency of diagnostic groups was similar for ea method. No significant difference was found in sensitivity (convention slide cytology 86 per cent versus *Cytospin 82 per cent), specificity (7* versus *82 per cent) or diagnostic accuracy (88* versus *91 per cent). Th Cytospin technique compares favourably with conventional sli cytology and can be recommended for ease of use in breast cytodiagnosi*

Fine-needle aspiration cytology (FNAC) has simplified decision making in the breast clinic. The collection of specimens and preparation of slides requires a level of experience that may not be freely available at all times. Technique is all important and a poor-quality smear may hamper diagnosis.

A method is described that allows collection of the whole aspirate into an alcohol-based transport medium, Cytospin fluid (Shandon Scientific, Runcorn, UK). The resulting suspension can be processed in the laboratory under ideal conditions, immediately or after a period of storage. This technique of slide production for cytological analysis was compared with conventional slide cytology.

Patients and methods

A total of 388 patients were studied in a symptomatic breast clinic over a 12-month period. Aspirates were taken from breast lesions by multiple passages (more than ten) of a 21-G needle attached to a 20-ml syringe with a vacuum applied, using the 'braced thumb' technique[1]. Immediate smears were made in 187 consecutive patients by a cytology medical laboratory scientific officer (MLSO) in the clinic and 'wet fixed' in alcohol before transport to the laboratory. The specimens were then stained with haematoxylin and eosin.

FNAC specimens from a further 201 consecutive patients were suspended by the clinician in Cytospin fluid. This consists of 95 per cent ethyl alcohol and 2 per cent polyethylene glycol (the alcohol acts to preserve nuclear and cellular morphology and the polyethylene glycol prevents dehydration). If kept at 4°C, samples may be processed at any time up to 48 h after aspiration. The solution was rinsed in and out of the barrel and needle three times to remove any adherent cells. The resulting suspension was centrifuged in a universal container for 10 min at 2500 r.p.m. (920*g*; Autobench Centrifuge, Baird and Tatlock, Romford, UK) and the cell pellet resuspended in a specially designed conical cuvette with a side arm. This was applied to a slide coated in poly-L-lysine with a layer of blotting paper in between. The composite apparatus was centrifuged at 1500 r.p.m. (200*g*) for 3 min in a Cytospin C3 centrifuge (Shandon Scientific). The centripetal force results in movement of cells from the apex of the cone along the side arm to the slide. The method allows aliquots of cells to be processed in a number of different ways, if required.

Haematoxylin and eosin stained smears were classified as benign, malignant, suspicious or unsatisfactory.

Results

Cytological examination of aspirates collected in Cytospin fluid showed a similar distribution of diagnostic groups compared with those processed by conventional slide cytology (*Table 1*). Unsatisfactory smears were reported with equal frequency for each method, making any 'learning curve' bias in favour of Cytospin unlikely. Trainees produced the highest number of unsatisfactory specimens in each group.

Of patients investigated by aspiration cytology a total 119 underwent open biopsy, allowing comparison of t preoperative cytological diagnosis with the formal histologic diagnosis for each cytological technique. Carcinoma w confirmed in all 26 patients with malignant aspirates, compar with seven of 14 with suspicious smears (conventional cytolog three; Cytospin, four). Four of 61 patients with benign cytolo were found to have breast cancer (conventional cytology, tw Cytospin, two), giving a false-negative rate of 7 per cent. Bo methods produced a similar number of unsatisfactory smea (*Table 2*). The use of Cytospin was associated with an increa in diagnostic accuracy compared with conventional sli cytology, but this was not statistically significant (*Table 3*).

Table 1 *Diagnostic groups for each method*

Diagnosis	Conventional slide cytology	Cytospi
Benign	97	109
Malignant	39	33
Suspicious	14	22
Unsatisfactory	37	37
Total	187	201

P not significant between methods ($\chi^2 = 2{\cdot}5$, 3 d.f., $P = 0{\cdot}48$)

Table 2 *Cytological* versus *histological diagnosis in 119 patients*

Diagnosis	Conventional slide cytology	Cytospi
Benign	33 (2)	28 (2)
Malignant	16 (16)	10 (10)
Suspicious	8 (3)	6 (4)
Unsatisfactory	11 (1)	7 (1)

Values in parentheses are numbers of patients with cancer diagnose histologically

Table 3 *Clinical utility of each method*

	Conventional slide cytology	Cytospi
Sensitivity	86	82
Specificity	72	82
Positive predictive value	100	100
Negative predictive value	94	93
Diagnostic accuracy	88	91

Values are percentages

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iscussion

ine-needle aspiration as a method of acquiring biopsy material as first proposed in 1904 to sample lymph nodes in sleeping ckness[2]. Martin and Ellis[3] described the technique more fully 1930, but it has received limited attention until relatively cently.

The value of cytology has become firmly established in the st decade and several studies have attested to its accuracy d importance in the diagnosis of breast disease[4–6]. The nventional technique demands immediate preparation of des from the aspirate and is highly operator dependent. It quires a skilled clinician or cytology MLSO to produce a near of optimal thickness[7] that can be assessed on-site for llularity. There is evidence to suggest that air drying, which ay occur in conventional slide cytology, can lead to orphological changes and the potential for artefacts[8]. oncern has been expressed at the potential risk of infection e to aerosol formation created by ejection of a sample on to slide in conventional cytology[8]. Current financial restrictions thin the National Health Service limit the availability of LSOs to all but specialist units.

The use of a liquid suspension medium overcomes many of ese problems. Little skill is required to deliver the aspirate to a universal container and the resulting suspension can be ed to lavage the needle and syringe to maximize the harvest cells for analysis. The aerosol effect is avoided and, once llected, samples can be stored at 4°C and processed under eal conditions at a convenient time. Results can be obtained thin 30 min, allowing early discussion of the findings with e patient if required. A trained cytology MLSO is not required the clinic, and this is an obvious benefit in units with limited affing and financial resources.

A significant proportion of aspirate may adhere to the needle d syringe, thereby reducing the cellular yield. The act of ashing the syringe may increase the yield and thus the clinical ility of an aspirate, allowing several slides to be produced om a single sample. Cells may be fractionated to allow munocytochemical analysis and flow cytometry, both of hich may yield further prognostic information[9]; conventional de cytology requires the harvesting of separate samples for ch investigation, thus increasing patient morbidity.

The Cytospin technique provides a useful alternative to conventional cytology in a symptomatic breast clinic. It provides a level of diagnostic accuracy similar to that reported in studies using the conventional method[10,11], but confirmation by a prospective randomized study comparing the two techniques is awaited.

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Use of silicone implants after wide local excision of the breast

The appearance of the breast after wide local excision for carcinom may be unsatisfactory. In 59 patients undergoing wide local excision silicone prosthesis was inserted into the cavity at the time of primar surgery. Assessment of the cosmetic result was performed after 1 months by questionnaire and clinical examination. Four prostheses wer removed within 1 year because of infection (two patients), woun breakdown (one) and pain (one). Seven prostheses were subsequentl removed because of severe capsular contraction. Capsular contractio was more common in patients who had received radiotherapy. Only 2 patients found the results of the implant acceptable or satisfactory. Th immediate use of intramammary implants after wide local excision currently associated with a poor cosmetic result, and the problem of th distorted breast after such excision requires continued attention.

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Wide local excision with adjuvant radiotherapy is a safe alternative to mastectomy in patients with early breast cancer[1]. Adequate clearance of the tumour may, however, require excision of large volumes of breast tissue resulting in considerable deformity, particularly for tumours in the medial and lower segments[2]. Subsequent radiotherapy may make the appearance of the breast worse[3]. The likelihood of a poor cosmetic result leads some surgeons to recommend mastectomy rather than wide local excision or to reduce the macroscopic margins of clearance, thereby increasing the risk of local recurrence[4].

This study examined the feasibility of using intramammary implants at the time of wide local excision of primary breast tumours.

Patients and methods

Since January 1987 patients have been offered a silicone implant at the time of wide local excision where indicated. Those in whom a prosthesis was inserted as a secondary procedure, following mastectomy, or for simple augmentation were not included. Informed consent to the insertion of the prosthesis was obtained in all patients but the final decision was taken by the surgeon during the operation.

The aim of surgery was to achieve at least 2 cm of macroscopic clearance. Resection margins were examined immediately by frozen section and further resection performed if necessary. Axillary dissection up to the insertion of the pectoralis minor (level I) was performed in all patients through a separate axillary incision.

A variety of gel-filled silicone implants was used, selected according to the volume of the resected specimen and placed within the excision cavity. A suction drain was used to drain the breast and axillary wounds, which were closed in two layers with 2/0 chromic catgut and 3/0 subcuticular polypropylene. Perioperative antibiotics were given and continued until the drain was removed, usually at 5 days.

Patients who had complete excision of the primary tumour received adjuvant chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil) or tamoxifen according to the oestrogen receptor status of the tumour. Radiotherapy was given to the breast and axilla in node-positive patients as 54 Gy in 27 fractions over 5 weeks. Patients with incomplete excision of the primary tumour received radiotherapy as above with an additional 10-Gy fractionated boost to the tumour bed.

Patients were reviewed at 2, 6 and 12 weeks and at 3-month intervals thereafter. The median follow-up was 38 (range 24–60) months. Assessment of the cosmetic result was performed at least 12 (range 12–48) months after insertion of the prosthesis by a specialist nurse and a doctor. The texture of the breast was classified according to a modification of Baker's classification[5] and patients asked to complete a questionnaire. Replies were assessed using the following scorin system, where 0 was the least satisfactory: general appearance of tl breast (0–5), shape (0–2), size (0–2), texture (0–3) and whether t breast was painful (0–4). This gave a maximum possible score of 1

Results

Between January 1987 and January 1990, 59 patients of mea age 51·9 (range 25–70) years undergoing wide local excisio of a primary breast tumour received a silicone implant. Th was a subgroup of 298 women who underwent wide loc excision during the same period. On the basis of frozen-sectio analysis 12 patients underwent further excision at the time primary resection. *Table 1* shows the total volume of brea tissue resected in relation to the macroscopic size of the primar tumour.

Histological examination showed invasive ductal carcinom in 47 patients (80 per cent); 28 had associated *in situ* diseas Ten patients (17 per cent) had lobular carcinoma and one medullary carcinoma. The remaining patient underwent central resection for Paget's disease of the nipple; histologic analysis showed intraductal changes only. Histologic clearance was obtained in 51 patients (86 per cent). Of th eight women with incomplete excision margins, four had *in sit* disease associated with an intraductal carcinoma, one ha multicentric invasive ductal carcinoma and the remaining thre had lobular carcinoma.

The sizes of the prostheses are shown in *Table 2*. In mo patients the volume of breast tissue resected was considerabl larger than the prosthesis. Thirty-eight patients (64 per cent received standard radiotherapy and five of the eight wit incomplete excision were given an additional boost to th tumour bed. Three patients died during follow-up, at 12, 1 and 24 months, and are not included in the subsequent analysis

Prostheses were removed in 11 patients (*Table 3*). Thre were removed within 3 months of insertion: two because infection and one after wound breakdown during radiotherap

Table 1 *Tumour size and volume of breast tissue removed*

Tumour diameter (cm)	No. of patients	Mean (range) volume of breast tissue excised (ml
0–1·9	13	149 (45–400)
2·0–5·0	34	234 (55–420)
>5·0	12	310 (162–720)

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ble 2 *Prosthesis size and volume of breast tissue removed*

rosthesis lume (ml)	No. of patients	Mean volume of breast tissue excised (ml)
70	3	70
80	27	200
90	14	205
100	6	231
110	3	239
120	6	242

ble 3 *Details of prostheses removed from 11 patients*

tient	Radiotherapy	Time since insertion (weeks)	Complication	Replaced
	Yes	10	Extrusion	No
	Yes	52	Hard, painful, failed manipulation	No
	Yes	100	Hard, painful, failed manipulation	No
	Yes	20	Painful breast	Yes
	Yes	1	Infected	No
	Yes	92	Hard, painful	Yes
	No	60	Hard, painful, failed manipulation	Yes
	Yes	68	Extrusion	No
	Yes	122	Hard, painful	Yes
	Yes	10	Infected	No
	Yes	59	Hard, painful	Yes

ble 4 *Late results of surgery in 52 patients*

	Baker grade	No. of patients	No. of patients who received radiotherapy
ormal texture	1	10	3
rm, normal appearance	2	17	9
rm, abnormal appearance	3	14	11
istorted, painful*	4	11	8

Prosthesis removed in six patients

able 5 *Results of the questionnaire in 40 patients*

ore	Result	No. of patients
–4	Awful	4
5–8	Poor	13
–12	Acceptable	16
–16	Satisfactory	7

he prosthesis was removed in 11 of the 59 patients, five did not reply d three had died

ne patient, who received radiotherapy, had a prosthesis placed because of recurrent pain in the breast. In seven atients the prosthesis was removed after more than 1 year and x of these had severe capsular contraction. Four of these atients had a new prosthesis inserted after partial excision of e fibrous capsule. In the remaining patient the implant started truding 68 weeks after insertion. This prosthesis had a volume 270 ml and was the largest of those used in the series. xcluding the three deaths and four early failures the results surgery were assessed using Baker's classification (*Table 4*). he results of the patient questionnaire are summarized in *able 5*.

One patient who had the prosthesis removed after 12 months ubsequently developed local recurrence and underwent astectomy. The original histological examination had shown multicentric invasive ductal carcinoma and the woman had received radiotherapy. Four patients developed distal recurrence and two a second primary in the contralateral breast.

Severe capsular contraction (Baker grade 3 or 4) occurred more often in patients undergoing postoperative radiotherapy: 19 of 32 women receiving radiotherapy *versus* six of 21 who did not.

Discussion

The aim of conservative resection for breast cancer must be to ensure complete excision of the tumour without removal of the whole breast. Lumpectomy may result in inadequate resection, and wide local excision or quadrantectomy may leave a distorted breast. Veronesi *et al.*[4] reviewed the results in women with tumours <2.5 cm in size undergoing lumpectomy or quadrantectomy. Resection margins were positive in 16 per cent of lumpectomy specimens *versus* 3 per cent of quadrantectomy specimens and this was associated with a higher local recurrence rate, 7 *versus* 2 per cent. The wider excision, however, gave poor cosmetic results with 21 per cent of patients undergoing quadrantectomy having significant distortion of the nipple–areola complex *versus* 7 per cent of those having lumpectomy.

Previous studies have shown that a poor cosmetic result is more common when >70 ml breast tissue is removed[6]. In the present study the size of the resected specimen varied between 45 and 720 (mean 205) ml and the volume of breast tissue excised increased with the size of the tumour. Larger volumes of tissue were removed in patients with *in situ* disease surrounding invasive ductal carcinoma. Disease-free primary excision margins were achieved in 86 per cent of patients, a value that compares favourably with those in previous studies[4].

In most patients the volume of tissue resected was considerably larger than the volume of the prosthesis inserted. In patients undergoing prosthetic reconstruction following mastectomy for carcinoma, larger prostheses are associated with a higher risk of failure[6]. In nine patients in the present study the implant was marginally larger than the resected specimen. The result was satisfactory (Baker grade 1 or 2) in six patients but in three, all of whom received radiotherapy, the prosthesis had to be removed.

Initially, smooth prostheses were used but in the latter part of the study textured-surface implants were introduced because of the reported lower incidence of capsule formation[7].

In common with breast reconstruction after mastectomy[8], capsule formation and contraction was the major problem. Severe capsular contraction, defined as Baker grade 3 or 4, occurred in 25 patients (47 per cent). Submuscular implantation may give a lower rate of contraction than the submammary site[8] but is not a practical option in patients undergoing wide local excision.

The most important finding of the present study was that severe capsular contraction occurred significantly more often in patients after radiotherapy. Animal studies suggest that radiation has no effect on implant capsules[9] but the results were analysed after only 6 months and the animals received a dose of only 30 Gy. A small retrospective study in humans has suggested that irradiation immediately after insertion of a breast implant may produce poorer cosmetic results[10].

Susceptible patients will develop capsular contraction within the first year[5] and this was confirmed by the present study. The six patients classed as Baker grade 4 who required prosthesis removal presented with problems within the first 6 months. Four of these patients with a prosthesis reimplanted now have a satisfactory result at a mean follow-up of 25 (range 16–33) months.

Only 23 of the women who answered the questionnaire found the results of the implant acceptable or satisfactory. A common concern was that the presence of the implant would make the diagnosis of recurrent tumour more difficult. It has been shown, however, that mammography is still reliable in patients with implants.

The use of intramammary prostheses after wide local excision for breast cancer is associated with a high rate of complications and poor cosmetic results, especially if radiotherapy is given. Improvements in prosthesis design such as surface texturing have reduced the rate of capsular contraction in patients undergoing reconstruction after mastectomy and might make intramammary implantation after wide local excision an acceptable procedure.

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Announcement

Eurosurgery 93 – 14–17 September 1993
Poster Competition for Surgical Trainees

The organizing committee of Eurosurgery 93 wishes to announce a poster competition, with a prize of 700 ecus (approximately £500) and a commemorative medallion. This competition is open to trainees in any surgical specialty for a poster presented at Eurosurgery 93.

Abstracts are invited from all trainees; those who have already had a poster accepted at the meeting will automatically be eligible for the prize. Trainees who wish to present a poster for this prize should write for further details and registration forms to Rebecca Baldry, Eurosurgery Organizing Committee Secretary, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK. Fascimile: 071 831 9438.

Abstracts, of not more than 200 words and clearly labelled 'Trainees' Poster Competition', should be sent to Rebecca Baldry at the Department of External Affairs at the College by 25 August 1993.

Registration at the meeting for trainees will be at the reduced rate of £90 per day or £250 for the full 3 days of the meeting.

Accommodation is available to trainees at the modest cost of £60 for 3 nights' bed and breakfast.

J. P. S. Lumley

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1-873

Randomized trial of laser scalpel for modified radical mastectomy

The efficacy of a contact neodymium yttrium–aluminium–garnet laser scalpel was assessed during breast surgery. Forty consecutive women undergoing modified radical mastectomy were randomized to operation performed with a conventional or laser scalpel. The laser scalpel was associated with a significant reduction in mean operative blood loss (149 versus *421 ml; 95 per cent confidence interval of difference 176–368 ml,* $P < 0{\cdot}001$*), but the mean operating time was longer (105* versus *80 min; 95 per cent confidence interval of difference 16–34 min,* $P < 0{\cdot}001$*). No significant differences were found in the volume of postoperative wound drainage, incidence of axillary seroma, postoperative pain score or time to return of shoulder mobility. Use of a laser scalpel in breast surgery cannot be recommended.*

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is claimed that surgical procedures performed with a laser alpel are more haemostatic and quicker than those using ·nventional techniques. They are said to be relatively pain-e, associated with increased postoperative mobility, reduced)und drainage and faster return to normal activity[1–3]. These ‹alities should be particularly attractive to surgeons ·rforming modified radical mastectomy because this operation frequently associated with a marked degree of blood loss, olonged wound drainage, axillary seroma and restriction of oulder movement[4].

The neodymium yttrium–aluminium–garnet (NdYAG) ser (wavelength 1064 nm) when used in contact mode is aimed to possess the benefits of a laser scalpel with the dvantage of having tactile feedback not possible with ɔn-contact laser beams[5]. The potential advantage of this laser alpel was assessed during modified radical mastectomy.

·atients and methods

itients

ɔrty consecutive women with breast cancer undergoing modified dical mastectomy were randomized to have surgery performed using conventional or laser scalpel. Randomization by sealed envelopes aced 20 patients into each arm. The groups were similar for age, age of tumour, body-weight and breast weight (*Table 1*). The study ıd the approval of the hospital ethics committee.

ıser

he system was a CL60 NdYAG laser with a 600-μm diameter quartz re and an ERP4 artificial sapphire contact frosted laser scalpel urgical Laser Technologies, Malvern, Pennsylvania, USA). The fibre ıd sapphire scalpels were cooled by coaxial air. The initial laser power tting was 12 W but this was increased until the desired cutting effect as achieved, usually no greater than 15 W. Operating theatre staff ıd the patient wore protective eyewear and the laser was operated in cordance with safety guidelines[6].

perative technique

women receiving laser dissection the initial skin incision was by ɔnventional scalpel because a thermal incision results in a poor ɔsmetic scar[7]. The laser scalpel was used for the remainder of the ssection including raising of the skin flaps. Mobilization of the breast om the chest wall, division of the pectoralis minor at its insertion, ssection around the axillary vein and level III clearance of the axillary ɔntents. Larger tributaries of the axillary vein and the occasional rger perforating branches of the internal mammary artery were ligated ɔnventionally. Haemostasis was otherwise achieved with the laser alpel. After all procedures the wound was lavaged with 0·1 per cent hypochlorite solution and one suction drain placed in the axilla and a second beneath the upper skin flap. The wound was closed with a subcuticular suture and covered with a clear plastic adhesive dressing.

Table 1 *Details of patients*

	Control group ($n = 20$)	Laser group ($n = 20$)
Age (years)*	56 (38–76)	59 (41–82)
Body-weight (kg)*	68·9 (50·8–82·5)	63·5 (44·5–101·0)
Breast weight (kg)*	0·91 (0·25–1·75)	0·66 (0·13–1·32)
No. with axillary node metastases	11	10
Tumour stage		
I	5	7
II	13	9
III	2	4

*Values are median (range)

Variables

Operative blood loss was measured by weighing all swabs. The weight of excised breast tissue and duration of the procedure were recorded. After operation the volume of wound drainage was noted and drains removed when the volume was <30 ml over the preceding 24-h period. Wound pain was assessed by linear analogue pain score on days 1, 3 and 5 after operation. Active shoulder movement was encouraged, all patients receiving daily physiotherapy. The return of shoulder movement was assessed daily and the endpoint for reasonable recovery of movement reached when the patient could fully externally rotate and abduct the shoulder so that the hand touched the back of the neck. The occurrence of any complication was noted, especially the incidence of axillary seroma. Seromas were aspirated aseptically and patients assessed weekly until complete resolution.

Statistical analysis

Statistical comparisons between the two groups were by Student's unpaired t test, with the exception of the incidence of axillary seroma which was subjected to Fisher's exact test.

Results

One patient was excluded from laser dissection because of equipment failure; the procedure was completed with a conventional scalpel. The laser scalpel aided haemostasis, although vessels >2 mm in diameter were more difficult to control and were best ligated. The mean blood loss was significantly less during laser dissection than during conventional surgery (149 *versus* 421 ml, $P < 0{\cdot}001$) (*Figure 1*). Laser procedures were noticeably more time consuming, with a mean

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ased on a presentation to the British Association of Surgical Oncology *‹ Sheffield, UK, July 1991*

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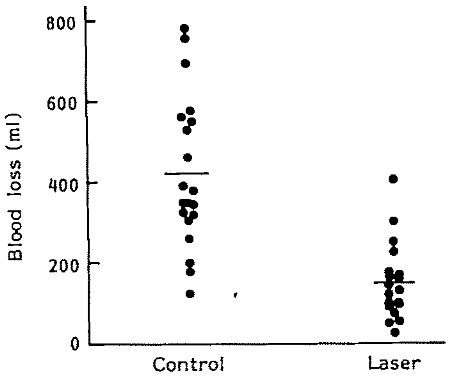

Figure 1 *Operative blood loss for conventional and laser surgery. Bars are means. The difference in sample means was −272 (95 per cent confidence interval −176 to −368) ml* (t = *2·03, 37 d.f.,* P < *0·001)*

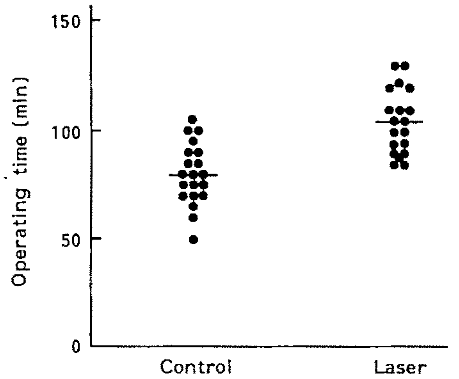

Figure 2 *Operating time for conventional and laser surgery. Bars are means. The difference in sample means was 25 (95 per cent confidence interval 16–34) min* (t = *2·03, 37 d.f.,* P < *0·001)*

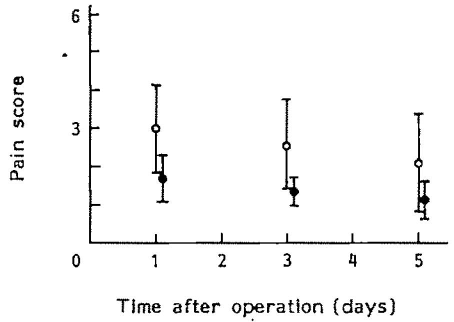

Figure 3 *Linear analogue pain scores after conventional* (o) *and laser* (●) *surgery on days 1, 3 and 5 after operation. Values are mean (95 per cent confidence interval).* P > *0·05 (Student's unpaired* t *test)*

Table 2 *Outcome of laser surgery*

	Control group ($n = 20$)	Laser group ($n = 20$)
Total wound drainage volume (ml)*	910 (380–2230)	880 (310–2440)
Time to return of shoulder mobility (days)*	4 (1–6)	3 (2–8)
Duration of hospital stay (days)*	7 (4–19)	7 (4–14)
No. with axillary seroma	11	10

*Values are median (range)

operating time of 105 min compared with 80 min for contro ($P < 0·001$) (*Figure 2*).

Linear analogue pain scores were not significantly differe in the laser group on each day after operation (*Figure 3*). The were no significant differences with respect to total postoperati wound drainage volume, time to return of useful should mobility, duration of hospital stay or incidence of axilla seroma (*Table 2*). There was one major complication: de vein thrombosis in one of the control patients. Min complications included wound sepsis with mild cellulitis arour the suture line or drain sites in five control patients and in s treated by laser. All episodes of sepsis resolved on oral antibiot therapy.

Discussion

Dissection was slower with the laser; this was not the result a 'learning curve' as technical experience had been achieve before the trial was begun. Excellent haemostasis and the clari of the operating field were impressive qualities of the las scalpel. This finding confirms previous reports of t haemostatic properties of the carbon dioxide laser during brea surgery[1]. Similar degrees of haemostasis, however, have be achieved by the use of electrocautery for dissection[8]; this h the disadvantage of muscle contraction, which is not a proble with the laser. The reported reduction in postoperative pa associated with laser procedures[1,3] was not confirmed by t present study.

Reports of reduced postoperative wound drainage and t elimination of axillary seroma following laser surgery[1,2] we also not confirmed. The volume of haemoserous woun drainage was considerable but similar in both groups. Axilla seroma developed in ≥50 per cent of patients in both group similar high incidences have previously been reported[9]. Serom may occur as a result of leakage from axillary lymphat vessels[10]. The NdYAG laser has been shown to seal lymphat vessels[11], but a high incidence of seroma was found in patien treated by laser. Seroma formation may be related to tiss trauma, the subsequent inflammatory response and th extensive area of the surgical wound[12]. Restricted should movement may have reduced the incidence of seroma. Acti movement was necessary to assess postoperative should mobility, the return of which was not influenced by surgic technique. An earlier return to normal daily activity with th laser[1,2] was not substantiated.

The frequency of minor complications was not reduced. A *in vitro* study suggested that the NdYAG laser scalpel may ha a sterilizing effect on incised tissue[13], but this did not reduc the incidence of cellulitis.

The contact NdYAG laser scalpel is an impressi haemostatic tool for soft tissue surgery, but no practical c clinical advantage could be demonstrated in the present stud The use of laser scalpels would not seem justifiable for routin application in breast surgery. They may help in cases where substantial degree of blood loss may occur during th procedure, or where blood loss is undesirable, for example i patients with human immunodeficiency virus infection.

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urgical workshop

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ew adjustable knot for ecuring subcuticular running tures

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bcuticular sutures are increasingly used for skin approxiation in clean surgery because of the superior appearance of e scar produced. New absorbable and non-absorbable onofilament sutures with improved handling properties have cently become available, further enlarging the scope for bcuticular closure[1,2]. As with all sutures, good tissue proximation with minimal tension is the key to sound wound aling and minimal scarring.

Several devices have become commercially available to cure the loose end of a running subcuticular suture, but a mple knot appears to be the cheapest and most practical ethod. A bulky knot will, however, cause an unsightly scar the end of the suture line and the knots currently used do t allow fine adjustment of the suture tension. For several ars the authors have adopted a new adjustable knot in n-absorbable subcuticular sutures that allows fine control of ture tension and minimal scarring.

urgical technique

fter the subcuticular suture is completed, its end is cut 10–15 cm from e cutaneous point of exit (*Figure 1a*). The redundant free suture is en tied around the end of the suture exiting the skin with a sliding ot made of two simple half-hitches (*Figure 1b*). This knot is slid ong the suture until it is against the skin. When the right tension on e suture is achieved, the sliding knot is secured in position by two tches between the exiting skin suture and the redundant suture.

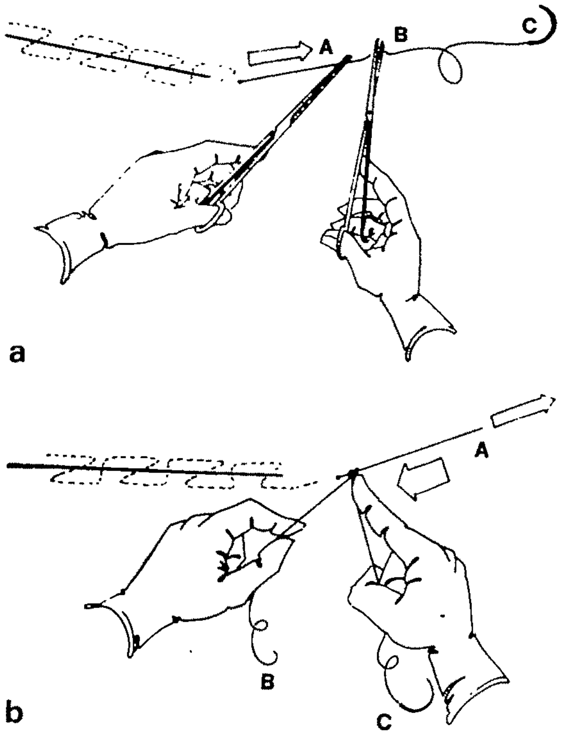

Figure 1 **a** *The subcuticular suture is completed and its free end divided to leave the suture exiting the skin (A) and a redundant suture (B–C).* **b** *The redundant suture (B–C) is tied around suture A with a knot that is slid along A until the skin is reached*

Discussion

The method described has been found to be simple and effective, leaving little or no scar at the end of the subcuticular suture line. This method can also be employed when a running suture breaks or knots itself accidentally in hand-sewn gastrointestinal or vascular anastomoses[3]. In such circumstances the broken end of a running suture can be joined in a similar fashion to a new running suture.

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Laparoscopic removal of an adrenocortical adenoma

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Primary aldosteronism is characterized by hypertension and hypokalaemia caused by excessive aldosterone secretion. A majority (80 per cent) of aldosterone-producing adrenocortical tumours are > 1 cm in diameter and are detectable by computed tomography (CT), magnetic resonance imaging and ultrasonography. For patients with unilateral adrenocortical adenoma, adrenalectomy should be performed. Until now, a laparoscopic approach to right adrenalectomy has not been described.

Surgical technique

A 33-year-old woman presented with a history of headaches and hypertension (blood pressure 180/100 mmHg). Biochemical studies showed a marked increase in aldosterone concentration to 63 (normal range 4–30) ng/dl and a low potassium level of 3·0 (normal range 3·5–4·5) mmol/l. A 1·8-cm tumour was detected by CT. Spironolactone, 200 mg daily for 2 weeks before surgery, corrected the hypertension and potassium deficiency.

The patient was positioned with an exaggerated lordosis and draped to allow immediate laparotomy if necessary. Pneumoperitoneum was established by puncture at the umbilicus and controlled electronically at a constant abdominal pressure of 13 mmHg. A straight telescope (0°) attached to a videocamera was inserted through a 10-mm cannula and abdominal exploration performed. Five other cannulas were then inserted as shown in *Figure 1*.

Operative exposure of the right adrenal gland commenced once the transverse colon and omentum had been carefully separated downward with an atraumatic angled dissector and the right and left lobes of the liver had been retracted anteriorly.

Once the overlying peritoneum lateral to the duodenum had been incised, careful dissection using an electrical hook coagulator freed the anterior and right sides of the vena cava. Gerota's fascia was opened and the fatty tissue attached to the adrenal gland was held up with a grasping forceps.

After identification of the renal vein, dissection was continued in a cephalad direction (*Figure 2*). The high-magnification image from the laparoscope facilitated dissection of the many branches from the renal artery and the main adrenal vein coming directly from the vena cava. All vascular elements were divided between clips.

Meticulous dissection using endoscopic scissors facilitated localization of a second adrenal vein entering the vena cava from the superior portion of the adrenal gland and arterial branches from the inferior phrenic artery, which were also clipped and divided. Attachments of the gland to the superior pole of the kidney were divided with a hook coagulator.

The right adrenal gland containing the tumour was then gently extracted via the umbilicus, which was widened slightly in a circular fashion to allow easier removal of the specimen.

The procedure lasted for 2 h 30 min. Histological examination showed an adrenocortical adenoma 1·8 cm in diameter.

The patient experienced minimal pain after operation, started a full liquid diet 24 h later, and was discharged 72 h after the procedure. She became normotensive and returned to full activity 5 days after operation.

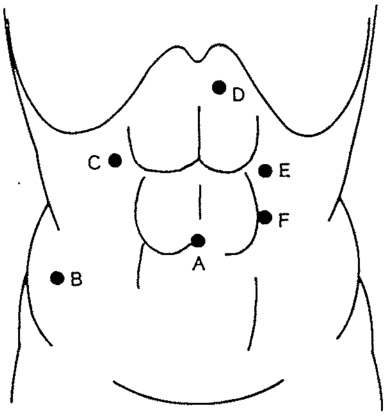

Figure 1 *Positions of the six cannulas. A, 10-mm umbilical cann B, 5-mm cannula at the anterior axillary site for the atraumatic grasp forceps; C, 5-mm cannula in the mid-clavicular line, two finger-wi beneath the right costal margin, for the palpation probe; D, 5-mm cann to the left of the midline for the irrigation–suction tube; E, 10-mm cann in the mid-clavicular line for the atraumatic angled dissector; F, 10- cannula for the electrical hook coagulator, scissors and clip applicat*

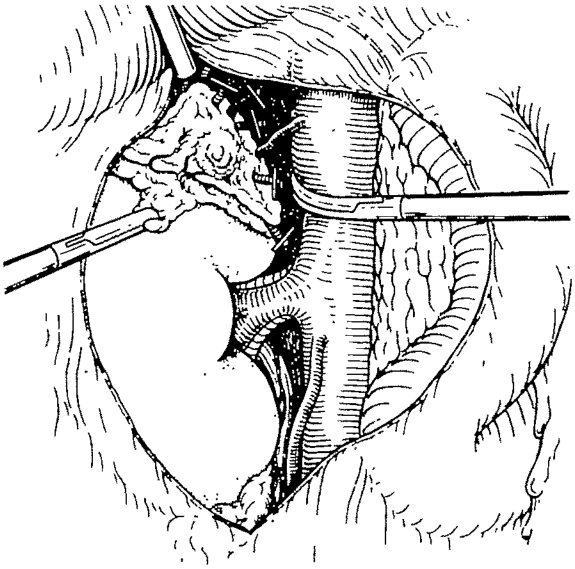

Figure 2 *To enhance visualization of the adrenal vessels the vena c was rotated medially with an angled dissector and by traction on fatty tissue attached to the gland*

Discussion

Over the years a number of open surgical approaches to t adrenal glands have been devised but laparoscopy offe obvious benefits.

The technique described has the advantage of avoiding t trauma and postoperative pain of open surgery, and allows short hospital stay with rapid return to full activity. Technicall dissection under videolaparoscopy is very selective because the optical enlargement; haemostasis tends to be perfect, wi minimal tissue trauma.

Acknowledgements

Figure 2 was drawn by Diane Kinton.

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Prospective randomized comparison of teres cardiopexy and Nissen fundoplication in the surgical therapy of gastro-oesophageal reflux disease

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Teres cardiopexy was compared with Nissen fundoplication in a prospective randomized study of surgery for gastro-oesophageal reflux disease refractory to medical treatment. Follow-up at 3 months of ten patients undergoing each procedure showed good clinical results and improvement of the mean symptom score in both groups, for cardiopexy from 7·8 to 1·1 ($P < 0.01$) *and for fundoplication from 5·7 to 0·2* ($P < 0.01$). *After 1 year, six of the ten patients undergoing cardiopexy required a second antireflux procedure because of recurrent disease, whereas one reoperation was performed after fundoplication. The mean symptom score after 1 year was higher in patients submitted to cardiopexy than in those receiving fundoplication (3·9* versus *0·3,* $P < 0.01$*). The mean endoscopic oesophagitis score after 1 year was no different from preoperative values after cardiopexy (1·9* versus *1·9) but was significantly lower after fundoplication (1·5* versus *0·3,* $P = 0.01$*). Ambulatory 24-h pH monitoring showed a significantly higher proportion of total time at pH < 4 after cardiopexy than fundoplication (24·0* versus *3·8 per cent,* $P < 0.05$*). Cardiopexy is significantly less effective than fundoplication for the treatment of gastro-oesophageal reflux disease assessed at 1-year follow-up. This study does not support the use of cardiopexy either in conventional or laparoscopic antireflux surgery.*

ost patients with gastro-oesophageal reflux disease (GORD) n be treated successfully by modification of lifestyle and edical treatment[1]. Maintenance therapy is mandatory since lapse usually occurs after discontinuation[1,2]; some patients ce lifelong medical treatment[3].

On the other hand, antireflux surgery can restore the mpetence of the lower oesophageal sphincter (LOS), and ter a successful procedure no further therapy is required[4,5]. me 35 years after its introduction, the Nissen fundoplication still the 'gold standard' for surgical treatment with which ewer techniques should be compared. Results of the Nissen rocedure reported in the literature are inconsistent and ostoperative sequelae include dysphagia and gas bloat; mplications such as gastric fistula have been reported[6,7]. ther techniques are constantly being developed or modified ut none has so far proven superior[2,8].

Narbona-Arnau and others have developed an antireflux rocedure that uses the ligamentum teres hepatis as a sling round the oesophagus to anchor the lower oesophagus into n intra-abdominal position. This procedure is known as teres ardiopexy[9–13]. This technique is thought to improve the astro-oesophageal valve mechanism and remarkable results ere reported in a retrospective study with only a 3–4 per cent ecurrence rate[12,13]. The procedure was associated with inimal morbidity and no long-term side-effects such as ysphagia and gas-bloat syndrome. The technique has never een validated by others or compared with different procedures.

After a pilot study in 30 patients the present authors found eres cardiopexy to be a technically feasible procedure with inimal postoperative morbidity and promising short-term esults. A prospective randomized trial was therefore initiated o assess the effect of teres cardiopexy compared with Nissen undoplication for the treatment of GORD refractory to medical therapy. The trial was discontinued when interim analysis showed a significantly higher rate of recurrence after cardiopexy at 1 year.

Patients and methods

Twenty patients, 14 men and six women of mean age 48 (range 24–64) years, were referred for surgical treatment of GORD resistant to medical therapy and entered the trial during the period February 1986 to February 1988. These patients all fulfilled the preoperative criteria. Ten patients were randomized to undergo cardiopexy and ten to Nissen fundoplication.

Patient selection

All patients had persistent symptoms of GORD even after intensive medical therapy for more than 6 months including at least 3 months of treatment with a H_2-receptor antagonist. None had undergone previous upper abdominal or oesophageal surgery, and ulcer disease and other gastric abnormalities were excluded by endoscopy. Patients with gallstone disease were excluded, as were those with abnormal oesophageal motility diagnosed manometrically and abnormal gastric emptying diagnosed by radionuclide scintigraphy.

Preoperative and postoperative evaluation

Preoperative and postoperative evaluation was carried out by symptom scoring at 0, 3 and 12 months, 24-h pH recording at 0 and 12 months and endoscopic assessment of oesophagitis at 0 and 12 months.

Symptoms. The symptom score was calculated by adding the scores for the four symptoms listed in *Table 1*. The maximum score was 13, the minimum 0.

Endoscopy. At flexible endoscopy the severity of oesophagitis was scored using the following system: 0, no oesophagitis; 1, erythema; 2,

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Table 1 *Symptoms and numerical scores according to severity*

	Score				
Symptom	0	1	2	3	4
Retrosternal pain	Absent	Once a day or less	Necessitating medical treatment	Disabling patient in daily living	—
Regurgitation	Absent	Once a day or less	Predictable at certain postures or after certain actions	Periods of aspiration or chronic cough	Recurrent periods pneumonia
Dysphagia	Absent	Once a day or less	Requiring liquids for swallowing	Periods of oesophageal obstruction	—
Heartburn	Absent	Once a day or less	Necessitating medical treatment	Disabling patient in daily living	—

The symptom score is the sum of scores for all four symptoms (maximum 13)

Table 2 *Preoperative findings for patients undergoing cardiopexy fundoplication*

	Cardiopexy ($n = 10$)	Fundoplicati ($n = 10$)
Sex ratio (M:F)	6:4	8:2
Mean (range) age (years)	51 (30–64)	45 (24–64)
Mean height (cm)	169	176
Mean weight (kg)	73·0	84·3
Mean duration of medical treatment (months)	25·4	32·6
Mean(s.e.m.) symptom score	7·8(0·87)	5·7(0·59)*
Mean(s.e.m.) endoscopy score	1·9(0·18)	1·5(0·27)
Mean(s.e.m.) percentage of total time at pH < 4	34·3(7·1)	16·4(2·4)†

* $P = 0{\cdot}06$; † $P < 0{\cdot}01$ (Student's *t* test)

linear erosions (maximum of three); 3, more than three erosions; and 4, stricture. Endoscopy was performed by an independent endoscopist, although the endoscopic views of cardiopexy and fundoplication are different and easily recognized.

24-h oesophageal pH recording. Continuous 24-h pH monitoring was performed with a glass electrode, connected in most patients to a portable recorder. The electrode was inserted through the nose and the tip positioned 5 cm above the LOS, as localized by manometry. Ambulatory 24-h pH recording was performed without treatment and without further restrictions at an outpatient setting. The percentage of the total time at pH <4 was used for comparison of results[14].

Surgical technique

All surgical procedures were performed by one surgeon at each of the three centres. Nissen fundoplication was performed as a floppy procedure, as described by Donahue and colleagues[15]. A midline upper abdominal incision was used. The oesophagus was mobilized and a crural repair performed if indicated. A complete fundal wrap was brought around the oesophagogastric junction and fixed to a corresponding fold of the fundus. A fundal wrap with a length of 4 cm was loosely constructed to allow the passage of at least an index finger within the fundoplication alongside the oesophagus.

Teres cardiopexy was performed according to the technique described by Narbona-Arnau and colleagues[12,13]. The original author visited the Netherlands before the start of the present study to explain and demonstrate this new technique. During a pilot study in 30 patients the surgical procedure was standardized according to a videotape produced by Narbona-Arnau. The oesophagus was mobilized in the same way as for the Nissen procedure and crural repair performed when indicated. The round ligament was mobilized, starting in the falciform ligament up to the umbilical insertion where it was divided. The ligament was passed dorsally to the oesophagogastric junction, around the oesophagus from right to left, and fixed to the cardia on both sides. The ligament was then fixed to the anterior gastric wall, parallel to the lesser curvature. Care was taken to preserve the vascular supply of the round ligament.

Randomization

Randomization was performed by the principal investigator (I. M. C. J.) 1 day before surgery by the drawing of envelopes. Stratification was performed for the participating hospitals. Informed consent was obtained from all patients entering the trial. It was originally suspected that the incidence of morbidity and/or side-effects, and probably also the recurrence rate, after cardiopexy would be lower than after the Nissen procedure, but the trial design allowed discontinuation on the basis of interim results.

Statistical analysis

Statistical comparison was performed with Student's *t* test; $P < 0{\cdot}05$ was taken to be significant.

Results

Preoperative evaluation

Preoperative findings for both groups are summarized in *Table 2*. There were no significant differences in age, weight, length of medical treatment and endoscopy score. The symptom score was slightly higher in patients submitted to cardiopexy but the difference was not significant ($P = 0{\cdot}06$). Th percentage of total time at pH < 4 was significantly higher i patients undergoing cardiopexy ($P < 0{\cdot}01$).

Surgical technique

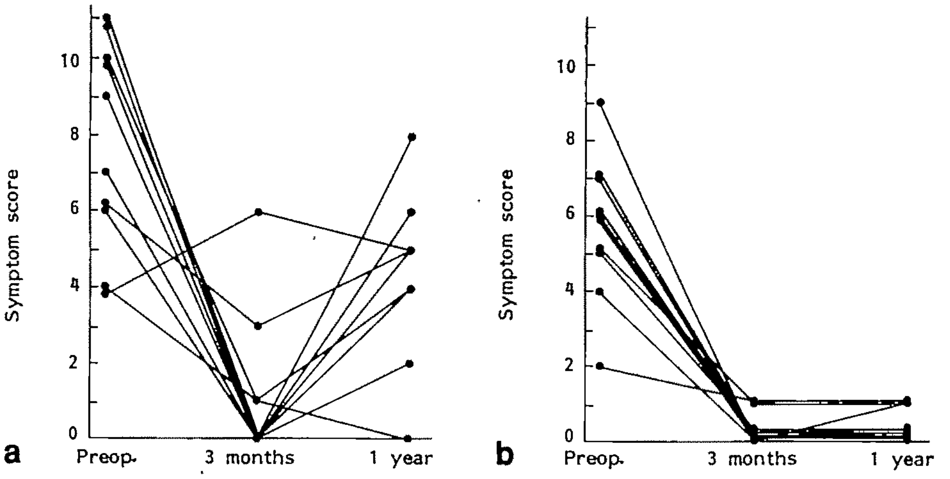
No technical problems were encountered during surgery. Bloo loss was 150 and 120 ml during cardiopexy and fundoplicatio respectively. Crural repair was performed in two patient undergoing cardiopexy and in five receiving fundoplication There was no death. Three patients undergoing cardiopex suffered from wound infection. The mean hospital stay wa similar in the two groups, 12·3 and 9·5 days after cardiopex and fundoplication respectively.

Symptoms

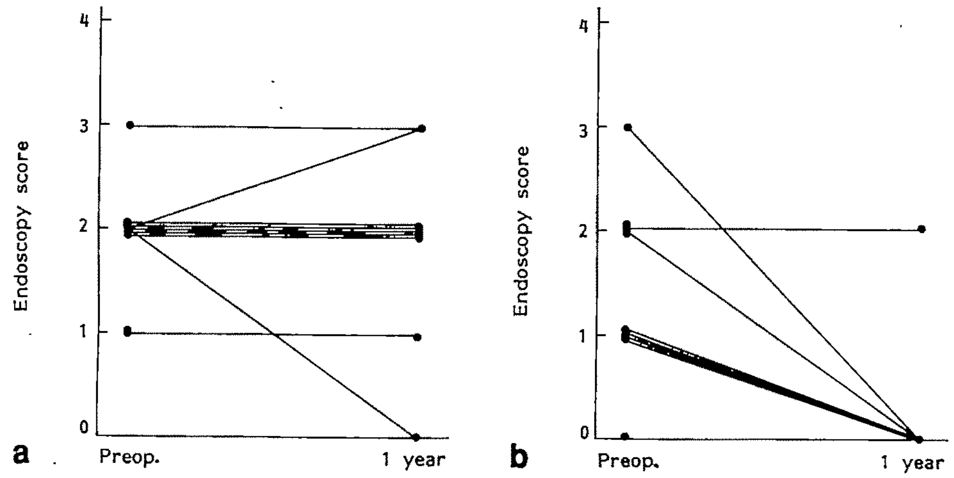
The mean(s.e.m.) symptom score had decreased significantl after 3 months in both groups (*Figure 1*) and was no differen in the two sets of patients (1·1(0·6) *versus* 0·2(0·1)). After 1 yea only two patients who had undergone cardiopexy had n symptoms and the mean(s.e.m.) symptom score was significantl higher than after fundoplication (3·9(0·8) *versus* 0·3(0·2) $P < 0{\cdot}01$). Seven patients who had undergone the Nisse procedure were without symptoms and three had one sympton less often than once a day. Significantly lower symptom score compared with preoperative values were found in both group after 3 months, suggesting a good short-term clinical result However, 1 year after surgery there was a significant increas in the symptom score after cardiopexy, whereas results afte fundoplication remained good (*Figure 1*).

Endoscopy

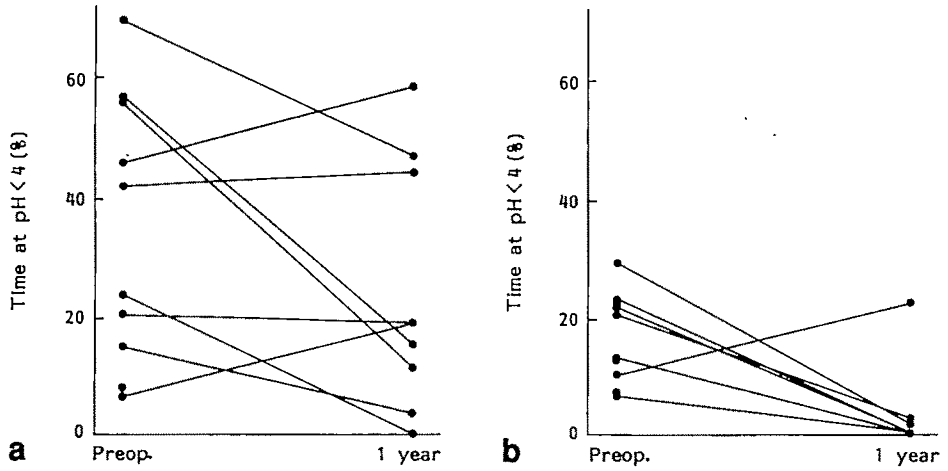
At 1 year, 16 patients (nine cardiopexy, seven fundoplication consented to evaluation by endoscopy. After cardiopexy only one patient had a normal oesophagus, whereas signs o oesophagitis were found in only one patient after fundoplication (*Figure 2*). Reduction of the mean(s.e.m.) endoscopy score was



gure 1 *Symptom scores for patients undergoing* **a** *cardiopexy and* **b** *fundoplication before operation, and 3 and 12 months after*



igure 2 *Endoscopy scores for patients undergoing* **a** *cardiopexy and* **b** *fundoplication before operation and 1 year after*



igure 3 *Percentage of total time at pH < 4 for patients undergoing* **a** *cardiopexy and* **b** *fundoplication before operation and 1 year after*

und only after fundoplication (0·3(0·3) *versus* 1·9(0·3), = 0·01).

4-h oesophageal pH recording

fter 1 year, 16 patients (nine cardiopexy, seven fundoplication) onsented to 24-h pH recording. The mean(s.e.m.) proportion f total time at pH < 4 was significantly higher after cardiopexy han fundoplication (24·0(6·9) *versus* 3·8(3·1) per cent, $< 0·05$). No reduction from preoperative values was found after cardiopexy, while a significant decrease was seen in patients submitted to fundoplication (*Figure 3*).

Follow-up

After 1 year, six patients who had undergone cardiopexy were reoperated on because of recurrent reflux disease with severe complaints despite conservative treatment. Fundoplication was performed without postoperative complications. One patient who had originally undergone fundoplication had abnormal findings on endoscopy (oesophagitis plus Barrett's oesophagus) and pH monitoring but a low symptom score; repeat fundoplication was performed after 1 year.

Monitoring of pH and endoscopy were not performed in three patients submitted to the Nissen procedure and in one who underwent cardiopexy; these patients were free from symptoms 1 year after surgery.

Discussion

In this study the symptomatic results were good at 3 months after both cardiopexy and fundoplication. These findings were similar to those from a pilot study in 30 patients (data not shown) performed before the prospective randomized trial was initiated. The satisfactory early results are very much in accordance with the literature and show the potential value of teres cardiopexy and fundoplication[12,13,16,17]. After 1 year, however, six of the ten patients who had undergone cardiopexy required a second antireflux procedure. The mean symptom score 1 year after cardiopexy was significantly higher than after fundoplication and also significantly higher than the value at 3 months. Objective criteria such as the degree of oesophagitis scored endoscopically and the percentage of total time at $pH < 4$ showed a significant difference between the two groups of patients, very much in favour of fundoplication. Findings at endoscopy and during 24-h pH recording had not improved 1 year after cardiopexy compared with preoperative results.

The disappointing outcome at 1 year after cardiopexy led to discontinuation of the trial after an interim analysis. Cardiopexy was, in the hands of the present authors, significantly less effective than fundoplication for the treatment of GORD. These findings are in sharp contrast to the excellent results reported by Narbona-Arnau *et al.*[12,13]. In that extensive experience with the technique, a low 3–4 per cent recurrence rate after 10–15 years of follow-up was reported. Some 10 per cent of patients had symptoms possibly related to reflux but no recurrence by objective criteria. Endoscopy and pH recording were performed after operation in 47 and 29 per cent of patients respectively, but results of these investigations are unfortunately not available.

The differences between the results of Narbona-Arnau *et al.* and those of the present study are remarkable and difficult to understand. They may be caused by technical aspects, despite the fact that experience was obtained in a pilot study. Three frequent technical errors are mentioned by Narbona-Arnau[13]: postoperative necrosis of the round ligament because of damage to the blood supply; poor fixation of the ligament; and poor positioning of the sling in the angle of His. These technical aspects were, however, extensively discussed before starting the present trial and one of the principal investigators attended nearly all the procedures during the pilot study and the trial. The acceptable results after 3 months also suggest that the initial procedure was performed correctly. Persistent traction on the ligament, in combination with constant movement in the area where the sling is located, could result in damage (possibly fibrosis) to the ligament after a longer period of time. A role for ischaemia or progressive lengthening of the round ligament has also been suggested[13].

Despite the negative results of the present trial the sling principle is an interesting new method. The procedure would be of more interest if the excellent results initially reported could be obtained by others, especially since postoperative morbidity in those studies was minimal[15–18].

The results of the present trial are also of special importance in view of recent developments in laparoscopic surgery, whi have led to the adaptation of the two techniques used f minimally invasive treatment of GORD[19,20]. Both techniqu have recently been described, and cardiopexy in particular c probably be performed laparoscopically without great difficul although the authors did not draw any conclusions regardi long-term benefits of the procedure[19,20]. The results of t present trial, however, suggest that more objective prospecti data should be obtained before teres cardiopexy can be advis for the surgical treatment of GORD, regardless of whether is performed by laparoscopic or open surgery.

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Erythromycin improves emptying of the denervated stomach after oesophagectomy

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Oesophagectomy, necessitating vagotomy, is associated with delayed gastric emptying. Cisapride and erythromycin have prokinetic effects and improve emptying of the innervated stomach. Their effect on the denervated stomach following oesophagectomy is unknown. The effect of pyloroplasty, cisapride and erythromycin on the rate of gastric emptying after oesophagectomy was studied using a radiolabelled meal. Oesophagectomy was associated with a marked delay in gastric emptying (56 per cent of the test meal remaining after 4 h) compared with age- and sex-matched normal controls (16 per cent; $P < 0{\cdot}001$*). Erythromycin improved the rate of gastric emptying to preoperative control values (18 per cent). Cisapride had no significant effect on gastric emptying. After pyloroplasty, 32 per cent of the label remained at 4 h (*$P = 0{\cdot}065$*). The mean(s.e.m.) half-emptying time in patients receiving erythromycin was 94(29) min, which was similar to control values, 55(3) min (*$P = 0{\cdot}26$*). Erythromycin may have a role in the treatment of gastric stasis following oesophagectomy or truncal vagotomy.*

sophageal resection necessitates complete vagotomy; some gree of gastric stasis is inevitable[1]. Postoperative symptoms aspiration, vomiting, postprandial fullness and heartburn cur[2]. The need for a drainage procedure in the totally gotomized intrathoracic stomach is controversial[3]. Some rgeons routinely perform pyloroplasty to prevent stasis[4,5], hereas others argue that the stomach drains adequately thout this procedure[6–9]. Pyloroplasty may result in tentially harmful bile reflux[10,11]. There is also a potential k of leakage from the additional suture line, and postprandial mping[12] and diarrhoea[13] may be promoted.

The prokinetic agent cisapride ameliorates delayed gastric ptying in the innervated stomach[14] but its role in the nervated stomach is less clear. Erythromycin, a macrolide tibiotic, has prokinetic effects in large animals[15] and diabetic tients[16] with delayed gastric emptying. The effect of ythromycin on the denervated stomach following oesophag- tomy has not been examined.

This paper studied the effect of oesophagectomy on gastric ptying and compared the effects of oral cisapride, oral ythromycin and pyloroplasty on postoperative gastric stasis.

atients and methods

he study was carried out over a 12-month period. Gastric emptying as examined in patients who had undergone oesophagectomy and sults compared with those from normal controls. Three methods of omoting gastric emptying were examined sequentially: pyloroplasty, rformed at the time of resection; oral cisapride; and oral ythromycin. Only patients who had undergone a three-stage resection taining the whole stomach (excluding the cardia) were studied. The omach was relocated intrathoracically in the posterior mediastinum. hree-stage oesophagectomy was chosen to evaluate gastric emptying it provided the largest and most uniform gastric remnant. All perations were performed by a single operator using a standard chnique[17].

At 3 months after surgery patients were readmitted for evaluation gastric emptying. Endoscopy was performed to exclude recurrence disease and patients with anastomotic stricture or recurrent tumour cluded.

tudy groups

atients were divided into the following groups: group 1 ($n = 10$), ormal controls; group 2 ($n = 16$), resection without adjunctive treatment; group 3 ($n = 6$), resection with pyloroplasty; group 4 ($n = 10$), resection with postoperative cisapride therapy; and group 5 ($n = 6$), resection with postoperative erythromycin therapy.

Control data were derived from an age- and sex-matched group of normal individuals with no previous history of intestinal surgery and normal endoscopy. Patients were not used as their own preoperative controls as luminal obstruction by the tumour might have produced a 'hopper effect' confounding the interpretation of gastric emptying. Patients did, however, act as self-controls when the results of prokinetic agents were examined after surgery.

The effects of the prokinetic agents were examined by studying patients before and after a 3-day course of treatment. Cisapride (10 mg orally) was given three times daily for 3 days with one dose on the morning of the study. Erythromycin (250 mg orally) was given three times daily for 3 days before the study with one dose on the morning of the study.

Test meal

The test meal consisted of 25 g scrambled egg-white labelled with technetium-99m tin colloid. This meal was smaller than that used in patients with an innervated stomach but pilot studies revealed excess delay when a larger meal was used, and such results were difficult to interpret.

Isotope study

After an overnight fast, the test meal was ingested within 3 min. Imaging of the gastric contents was started immediately and continued for 4 h at intervals (every 5 min for the first 30 min, decreasing to every 10 min for the next 30 min and every 20 min for the next 3 h). The radioactivity in the stomach at the first time interval was defined as 100 per cent and later activities compared with this value. Patients underwent imaging for 40 s with the data accumulated by a 20 per cent energy window peaked at 140 keV. Anterior and posterior images were obtained at each time interval and the site of the stomach and the distance from the camera compensated for.

Three parameters were determined from the data: the lag time (the period before radioactivity began to decrease), the half-emptying time (the period for the activity in the stomach to fall to 50 per cent once the lag phase was over), and the percentage activity remaining in the stomach at 4 h. Group mean values were calculated.

There was wide variability in lag time and half-emptying time in the postoperative group. Results are therefore reported as the percentage activity remaining at 4 h and the half-emptying time.

Data processing was performed blindly by an independent assessor who was not aware of the treatment.

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Statistical analysis

Paired data from the gastric emptying tests were analysed using the Wilcoxon signed rank test and unpaired comparisons made by the Wilcoxon rank sum test.

Results

Details of patients are shown in *Table 1*. In normal controls, 16 per cent of the meal remained in the stomach after 4 h (*Figure 1*). Oesophagectomy resulted in a significant delay in gastric emptying, with 56 per cent of the activity remaining in the stomach at the end of the study period ($P < 0{\cdot}001$). There was a reduction in the proportion of the meal remaining in the stomach after pyloroplasty to 32 per cent. This value was not significantly different from that observed in controls ($P = 0{\cdot}11$) or untreated patients after oesophagectomy ($P = 0{\cdot}065$) (*Figure 1*). In patients receiving cisapride, 49 per cent of the activity remained after 4 h, a value not significantly different from that obtained before treatment ($P = 0{\cdot}20$) (*Figure 2*). It was, however, significantly different from that in controls ($P = 0{\cdot}007$). After erythromycin therapy, the mean proportion of the meal remaining at 4 h was 18 per cent, similar to conti values ($P = 0{\cdot}11$) and a significant improvement on valu obtained before therapy ($P < 0{\cdot}02$) (*Figure 3*).

Lag times varied widely in the postoperative groups. T mean(s.e.m.) lag time in the untreated postoperative patie group was 54(20) min, similar to control values of 11(1) m ($P = 0{\cdot}19$). These values were similar to those in patien receiving cisapride (73(22) min; $P = 0{\cdot}13$), erythromyc (18(11) min; $P = 0{\cdot}13$) and pyloroplasty (62(37) mi $P = 0{\cdot}22$).

The mean(s.e.m.) half-emptying time in patients treated wi erythromycin was 94(29) min, similar to control values 55(3) min ($P = 0{\cdot}26$). Compared with controls, the ha emptying time in all patient groups after oesophagectomy w significantly raised: in untreated postoperative patients tl mean(s.e.m.) half-emptying time was 153(18) min ($P = 0{\cdot}0002$ in those receiving cisapride it was 114(15) min ($P = 0{\cdot}003$ and in patients who had undergone pyloroplasty t mean(s.e.m.) half-emptying time was 128(38) min ($P = 0{\cdot}05$

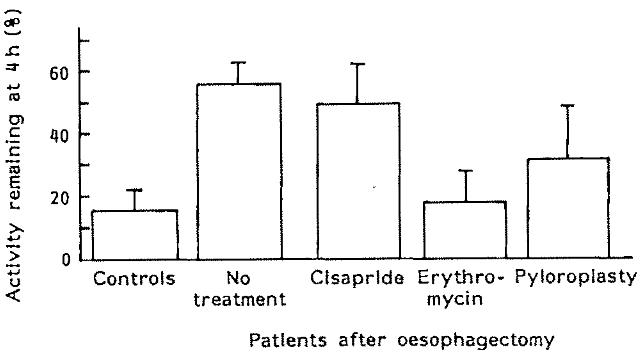

Figure 1 *Effect of different therapies on mean(s.e.m.) gastric emptying. Significantly increased delay was seen after oesophagectomy* (P < *0·001*) *and after cisapride* (P = *0·007*) (*Wilcoxon rank sum test*). *Erythromycin treatment allowed normal 4-hourly emptying*

Discussion

The quality of life for patients who have undergo oesophagectomy may be reduced by delayed gastric emptyin This may be apparent immediately after the operation wi prolonged nasogastric drainage and delayed resumption of or diet. It may be of greater significance after cervical anastomos as laryngeal protective mechanisms are impaired[18], increasin the risk of aspiration[2]. In the longer term, patients may troubled by a sensation of fullness, foul eructation and supi regurgitation[9,19].

Pyloroplasty did not significantly improve gastric emptyin in the present study. Mannell *et al.*[2], in a prospecti randomized trial using a radiolabelled meat meal, reported difference in gastric emptying in patients with and without drainage procedure evaluated 1–3 months after oesopha ectomy. By contrast, Fok *et al.*[20] found in a prospecti controlled trial that gastric emptying was significantly increase at 6 months in those with pyloroplasty. A dilute semisolid me was used to assess emptying[20], and this may have overestimate

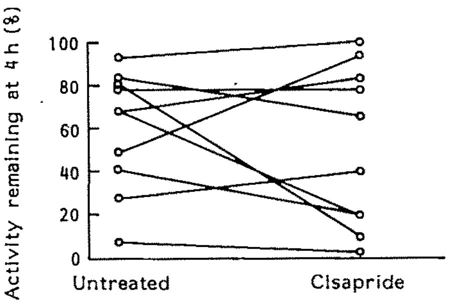

Figure 2 *Effect of cisapride in individual patients on delayed gastric emptying after three-stage oesophagectomy.* (P = *0·20, Wilcoxon signed rank test*)

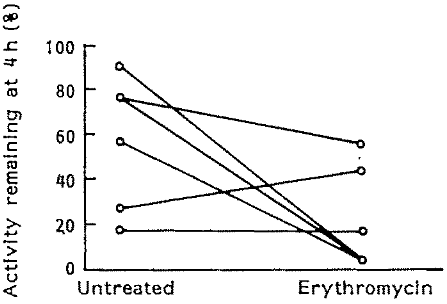

Figure 3 *Effect of erythromycin in individual patients on delayed gastr emptying after three-stage oesophagectomy.* (P < *0·02, Wilcoxon signe rank test*)

Table 1 *Details of patient groups*

		Patients after oesophagectomy			
	Controls ($n = 10$)	No treatment ($n = 16$)	Cisapride ($n = 10$)	Erythromycin ($n = 6$)	Pyloroplas ($n = 6$)
Mean age (years)	63	66	67	65	65
Sex ratio (M:F)	4:6	6:10	4:6	2:4	5:1
Adenocarcinoma	0	11	7	4	4
Squamous cell carcinoma	0	5	3	2	2

No treatment means no pyloroplasty or additional therapy was given to enhance gastric emptying. No significant difference was found betwee patient groups e rate. There is considerable evidence to show that vagotomy sults in enhanced emptying of liquids, as a result of loss of ccommodation and receptive relaxation[9], and in stasis of lids, because of lack of active propulsion[19,21]. Some 3 per cent of the patients without pyloroplasty experienced ostoperative gastric stasis but only one required reoperation[20].

The present failure of cisapride to influence emptying may e related to its mode of action. The drug enhances the release f acetylcholine in the myenteric plexus but also has a direct ction on gastrointestinal muscle *in vitro*[22]. The present study uggests that an intact vagal supply is necessary for its effects. ailure of action may be due to impaired absorption, onsequent upon delayed gastric emptying and compounded y food debris in the stomach.

Up to 95 per cent of subjects who receive intravenous rythromycin experience gastrointestinal symptoms[23], and a irect effect on gastrointestinal motility has been documented[24,25]. Erythromycin probably acts as a motilin receptor gonist[26]. Its main effect is to coordinate interdigestive motor omplexes and, in the animal model, these effects may be locked by nifedipine but not atropine, suggesting that they re calcium dependent but not vagally mediated[27]. Like isapride, erythromycin is absorbed in the upper small intestine, ut only the latter drug resulted in a significant increase in astric emptying in the present study, suggesting that it may lso have a local action on motilin receptors.

Numerous laboratory studies have confirmed an effect of rythromycin on gastric motility[28] but few reports of a herapeutic role have been published. Two studies found the rug to be of benefit in the treatment of diabetic gastroaresis[16,29]. Armstrong *et al.*[30] reported its effect in two atients with Ogilvie's syndrome and Miller *et al.*[31] found that t enhanced intestinal motility in patients with chronic intestinal seudo-obstruction. In the only other report of the use of rythromycin after vagotomy, a patient who had undergone esophagectomy had enhanced gastric emptying[32].

Gastric emptying in the present study was significantly elayed after oesophagectomy, and erythromycin therapy was he most effective method of correcting this delay. A motilin eceptor agonist without antibiotic effects would have a useful ole in the long-term management of postvagotomy gastric tasis.

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Oesophagomyotomy for achalasia: a 22-year experience

To determine the clinical results in achalasia, particularly as regard postoperative gastro-oesophageal reflux, a 22-year personal experience with transthoracic short oesophagomyotomy without an antireflux procedure was analysed. A total of 185 such procedures were performed of which 179 (97 per cent) were available for analysis. There was an overall improvement rate of 89 per cent over a mean postoperative interval of 9 years. Primary procedures were followed by a 93 per cen rate of improvement. Twenty patients, nine of whom had previously undergone one or more oesophageal operations, were considered a having a poor result. Marked gastro-oesophageal reflux accounted for a poor outcome in nine patients. Although the overall rate of postoperative improvement did not deteriorate significantly with time the level of improvement did, the proportion of excellent results declining from 54 to 32 per cent (P = 0·02) at 10–20 years after operation. These findings substantiate the view that a short transthoracic oesophagomyotomy without an antireflux procedure provides excellent long-term relief of dysphagia for the patient with oesophageal achalasia and is accompanied by an extremely low risk of serious postoperative gastro-oesophageal reflux.

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Heller's double cardiomyotomy, first performed in 1913, introduced the modern surgical era for the treatment of patients with oesophageal achalasia[1]. Since this original publication, the operation has undergone many modifications, the most important of which have been the use of a single instead of a double myotomy[2,3] and the addition of an antireflux procedure at the time of myotomy[4–6]. The latter modification remains a controversial addition which the present author has not supported: experimental[7] and clinical[8,9] evidence suggest that oesophagomyotomy performed transthoracically and limited for the most part to the distal oesophagus does not require an antireflux manoeuvre to achieve excellent results, including a low incidence of gastro-oesophageal reflux disease (GORD). I believe transthoracic short oesophagomyotomy without an antireflux procedure to be the primary treatment of choice for all symptomatic patients with oesophageal achalasia, and that it should be carried out early in the course of the disease before the development of megaoesophagus.

The purpose of this study is to review a 22-year personal experience with the operation with emphasis on the incidence of postoperative GORD. Also included is a summary of the long-term results in a small group of patients with a 10–20-year follow-up, to determine the risk of late clinical deterioration in those with initially good results (a study that has been published in detail elsewhere[10]).

Patients and methods

Clinical material

Between January 1970 and January 1992, 183 patients underwent 185 oesophagomyotomies of the distal oesophagus on the author's surgical service. Two patients required reoperation because of an initially inadequate myotomy. The sexes were equally divided, there being 90 male and 93 female patients of median age 42 (range 15–85) years. Symptoms of dysphagia had been present from 1 month to 60 years with a median duration of 3 years. Of the 185 procedures, 90 were preceded by definitive invasive therapy. Although many patients had a trial of peroral bougienage, a technique of little value in this disease, 60 had undergone forceful dilatation on one or more occasions and 3 patients, including two originally operated on in this department, had a previous operative oesophageal procedure (usually oesophagomyotomy). The extent of disease as defined radiographically was mild in 35 per cent, moderately severe in 37 per cent and severe in 28 per cent. Patients with a mild form of disease exhibited an oesophageal calibre <4 cm. Moderately severe disease required an oesophageal dilatation of 4–6 cm, while severe disease implied an oesophageal calibre >6 cm.

Surgical technique

The operative technique has been reported previously[11–13] and will only be summarized here. A thoracic approach is preferred, as it provides the best access to the lower oesophageal sphincter and minimizes the risk of postoperative GORD, which occurs more commonly when the transabdominal approach is used[8]. An incision is made through the bed of the non-resected eighth rib, the angle of which may be divided for better exposure. The mediastinal pleura is opened and the oesophagus is gently elevated by an encircling Penrose drain, care being taken to preserve the vagus nerves (*Figure 1a*). A longitudinal incision is made on the left anterolateral wall of the oesophagus for a distance of 6–8 cm limited for the most part to the distal oesophagus and extending on to the stomach for $\leqslant 1$ cm (*Figure 1b*). The incision is extended cephalad to include the dilated thick-walled portion of the oesophagus to ensure complete division of the circular muscle of the distal oesophagus (*Figure 1c*). The mucosa is permitted to bulge through the incision by freeing half the circumference of the mucosal tube from the overlying musculature to prevent subsequent healing of the myotomy (*Figure 1d*). A change in the mucosal vasculature from the pale oesophageal mucosa to the more vascular gastric mucosa tells the surgeon that the incision has reached the stomach, permitting too long a gastric extension of the myotomy to be avoided. The oesophagus is then returned to its bed, and the mediastinal pleura is closed over it with a running catgut stitch. When a widened hiatus or small hiatus hernia is present, the oesophagogastric junction is fixed subdiaphragmatically by two non-absorbable mattress sutures placed in the oesophageal wall near the oesophagogastric junction, on either side of the myotomy, and passed through the hiatus to be fixed to the undersurface of the diaphragm. The thoracic incision is then closed, and an intercostal catheter is left for postoperative drainage. Oral feeding is begun the following day and discharge from hospital is usually possible 4–7 days after operation.

Additional surgical procedures were used in 67 patients. The manoeuvre of subdiaphragmatic fixation of the cardia was performed in 43 patients. A small mucosal perforation was recognized and closed

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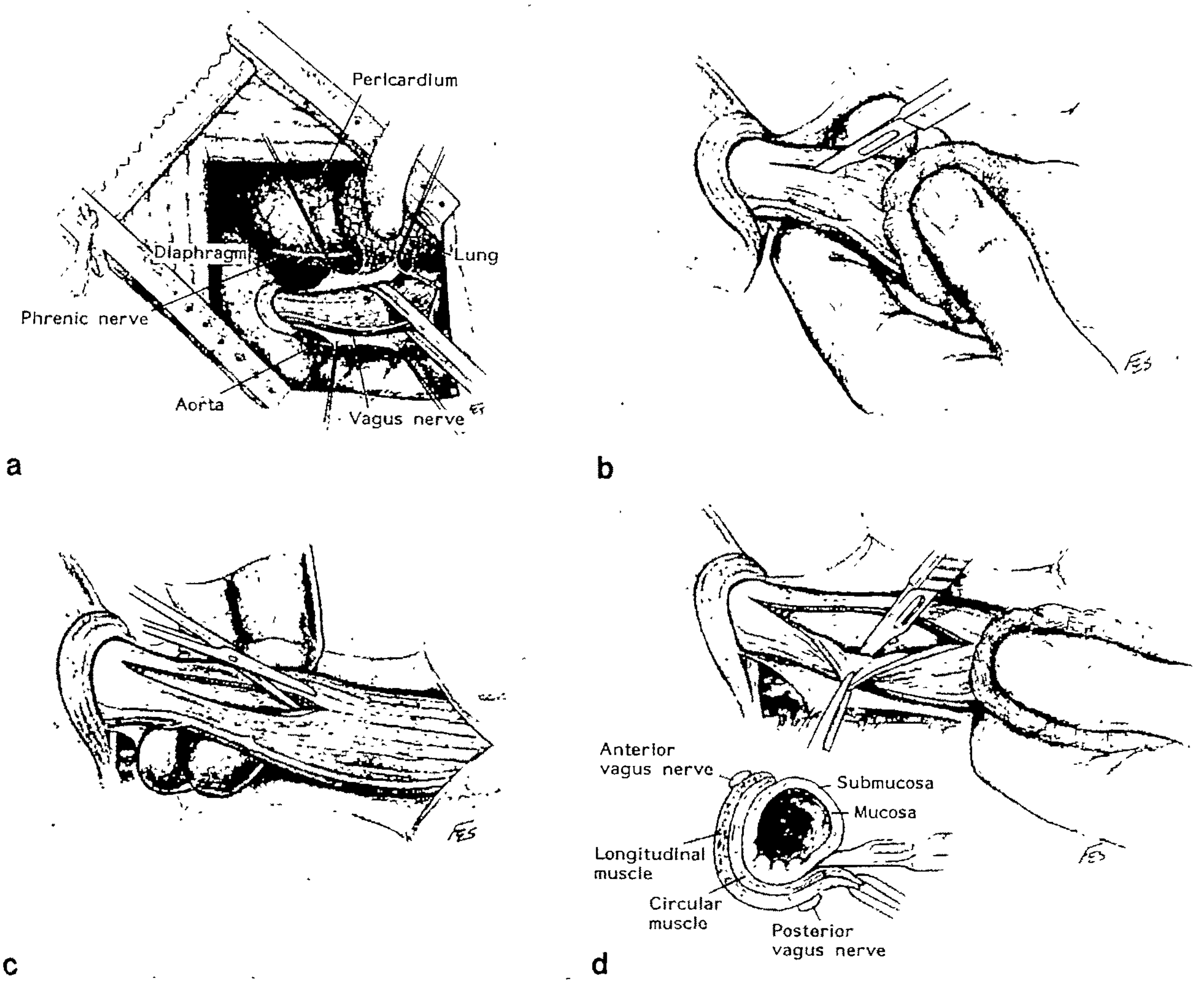

Figure 1 *Technique of transthoracic oesophagomyotomy.* **a** *Exposure of the distal oesophagus through a left-sided thoracotomy. The broken line indicates the site of proposed incision.* **b** *Initiation of myotomy.* **c** *Completion of myotomy.* **d** *Freeing of mucosa from overlying muscle.* (*From Ellis*[11]*; reproduced with permission*)

o 13. Four patients required concomitant excision of an epiphrenic diverticulum. Three with marked megaoesophagus underwent elliptical xcision of part of the lateral muscular wall of the oesophagus at the time of myotomy. Two patients with a duodenal ulcer had selective agotomy and pyloroplasty, while a fourth with severe megaoesophagus underwent segmental resection of the redundant sigmoid-shaped oesophagus with end-to-end oesophago-oesophagostomy at the time of myotomy. One of the three patients undergoing partial excision of he oesophageal wall also had a right lower lobectomy for oesophago-pulmonary fistula, a procedure that was the subject of a previous publication[14].

Results

There were no hospital deaths, but 16 patients (9 per cent) had complications. Five patients required bronchoscopy because of retained secretions, one of whom developed frank pneumonitis. A urinary tract infection developed in four patients, a wound nfection in three and spontaneous pneumothorax occurred in a further two. A paraoesophageal hiatus hernia requiring surgical correction developed after operation in one patient, a complication that has been reported by others[15,16], and a further patient had a small contained oesophageal leak in the mediastinum that healed spontaneously with hyperalimentation. The postoperative hospital stay ranged from 4 to 21 (mean 7) days.

Clinical results were evaluated on the basis of personal examination at a return medical visit or by communication (telephone or letter) with the patient, a relative or personal physician during the past 2 years. A modified Visick[17] scoring system was used to evaluate results. To qualify as having an excellent result the patient had to be asymptomatic. A good result was assigned to patients who had rare symptoms of dysphagia when under stress or eating rapidly. A fair result implied improvement of the patient's preoperative symptoms, but with residual symptoms of dysphagia. In addition, a patient who experienced reflux symptoms requiring medication was classified as having a fair result even though dysphagia was completely relieved. A poor result implied failure of the operation to relieve the preoperative symptoms or the development of new disabling symptoms.

The follow-up varied from 6 months to 20 years with a mean of 9 years. In all, 179 operations (97 per cent) were available for postoperative evaluation. Six patients were lost to follow-up and not included in the final analysis but, at the last evaluation 16 and 17 months after operation, two were classified as having excellent results. The results of nine patients lost to follow-up more than 5 years after operation were included, as were those in ten further patients who died from unrelated causes. One of these patients died from carcinoma of the oesophagus 4·5 years after myotomy with a good result before the development of cancer. This patient is one of eight encountered on this service during the period encompassed by this review who had oesophageal achalasia and subsequently developed oesophageal carcinoma. They will be the subject of a separate report.

Of the 179 operations available for review, 159 (89 per cent) were classified as successful, the patients having improvement in symptoms (*Table 1*). Results were excellent in 71 patients, good in 61 and fair in 27. Twenty of the operations resulted in

Table 1 *Results of oesophagomyotomy*

Result	Patients	Primary operations	Reoperations
Improved			
Excellent	71	66	5
Good	61	52	9
Fair	27	20	7
Total	159 (89)	138 (93)	21 (70)
Poor	20 (11)	11 (7)	9 (30)
Total	179	149	30

Values in parentheses are percentages

Table 2 *Causes of poor results after oesophagomyotomy*

Condition	No. of patients
Gastro-oesophageal reflux	9 (5)
Inadequate myotomy	5 (3)
Megaoesophagus	3 (2)
Poor oesophageal emptying	3 (2)

Values in parentheses are percentages

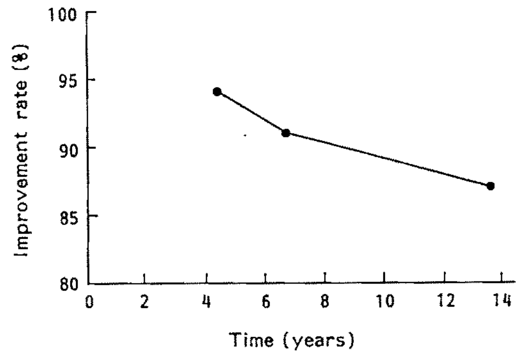

Figure 2 *Symptomatic improvement rate of patients with achalasia after oesophagomyotomy at mean follow-up intervals of 4·5 and 6·7 years, and at a median follow-up of 13·6 years. (Adapted from Ellis* et al.[10] *with permission)*

a poor outcome. Primary operations were accompanied by a 93 per cent improvement rate, compared with only 70 per cent after reoperative procedures.

It is important to scrutinize the reasons for a poor result (*Table 2*). Of the 20 patients so classified, nine had undergone previous oesophageal procedures. GORD was thought to have developed in nine patients, six of whom developed stricture, requiring oesophageal dilatation in five. Three of the nine patients ultimately required oesophagectomy and colon interposition, and one was treated with a Belsey antireflux procedure. Three of the nine who initially improved after operation developed reflux oesophagitis 6, 10 and 13 years later. Persistence of symptoms after operation in five patients suggested an inadequate myotomy as the cause. In two of these patients the original myotomy was performed by this service and the myotomy extended at a second operation; one of these had a good result. The remaining three, in whom the original myotomy was performed elsewhere, were not improved by extension of the original myotomy and one of these ultimately required a third operation. Classical megaoesophagus was considered responsible for poor results in three patients, two of whom required oesophageal resection and colon interposition. A further three patients were considered to have had a poor result because of poor oesophageal emptying, which developed 10 years after operation in two patients and 13 years after surgery in a third, who improved at first before developing recurrent dysphagia.

Preliminary findings in an earlier follow-up study suggested

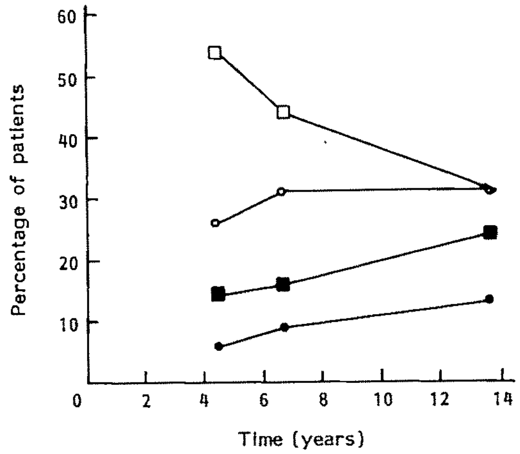

Figure 3 *Change in level of symptomatic improvement of patients w achalasia who underwent oesophagomyotomy.* □, *Excellent;* ○, *go* ■, *fair;* ●, *poor. (Adapted from Ellis* et al.[10] *with permission.)* P = *0* *(early excellent* versus *late excellent);* P = *0·05 (early fair and p* versus *late fair and poor); Miettenen's modification of Fisher's exact te*

late deterioration in results with the passage of time, althou the differences were not statistically significant[18]. For th reason, results 10–20 years after operation were analysed in patients operated on between 1970 and 1981 and reported detail elsewhere[10]. The findings in 68 of these patients w qualified for evaluation also disclosed no statistically significa difference between early and late improvement rates (*Figure* There was, however, a decline in the level of improvement, t proportion of excellent results falling from 54 to 32 per ce (*P* = 0·02) while that of fair and poor results together increas from 20 to 37 per cent (*P* = 0·05) (*Figure 3*). In this sm group of patients followed for a long period of time, t incidence of reflux oesophagitis was similar to that in the over experience now being reported (4 *versus* 5·0 per cent).

Discussion

The controversy regarding the need for an antireflux operati at the time of oesophagomyotomy for achalasia continues. T present results clearly show that a short transthorac oesophagomyotomy without an antireflux procedure is safe a has few postoperative complications. Since all of the procedur were performed transthoracically, a comparison between t incidence of complications following the transthoracic a transabdominal approaches is impossible. Although t reported incidence of complications following each of t approaches appears to be similar[8], there has been prospective randomized controlled study from a sing institution comparing morbidity after the two approache More importantly, the late results after oesophagomyoto performed by the technique described include a low inciden of significant gastro-oesophageal reflux. It remains the cas however, that other techniques of oesophagomyotomy ha results as good as those reported here. Under certa circumstances, it is essential that an antireflux manoeuvre performed. Use of the abdominal approach, as favoured most European surgeons[19], is an example. There is eviden that the incidence of GORD is higher after oesophagomyoto performed by this route than when the transthoracic approa is employed[8]. Therefore, if an abdominal approach is selecte an antireflux procedure is mandatory. When the myotomy performed transthoracically with a long incision on t stomach, an antireflux procedure is also essential. Not on does a long gastric myotomy interfere with the antirefl mechanism, perhaps by severance of the gastric sling fibres, b to expose the stomach to permit such a long extension of t myotomy, all the hiatal attachments of the oesophagogast area must be divided, making postoperative herniation mo likely.

A combined oesophagomyotomy–fundoplication manoeuv not without risk, for a patient with no oesophageal peristalsis n develop obstructive symptoms from too tight a wrap, articularly one of the Nissen type. Topart and associates[20] ointed out that, although early results after combined sophagomyotomy and Nissen fundoplication were satisfactory, late follow-up revealed increasing oesophageal tention with poor emptying and recurrence of symptoms. ccordingly, care should be taken to use a partial wrap, such the Belsey, Dor or Toupet procedures, if circumstances ctate the need for this ancillary manoeuvre.

Although the overall results of the combined operation are milar to those reported here, the incidence of postoperative ORD varies. Little and associates[6], using a transthoracic pproach combined with a Belsey procedure, reported a low cidence of GORD, although the precise value was not stated. onavina and colleagues[21] noted an 8·6 per cent incidence of flux after transabdominal myotomy combined with the Dor ndoplication. Stipa and associates[22] reported postoperative flux symptoms in 9·4–15·3 per cent of patients, depending on hether a complete (Nissen) or partial (Belsey) wrap was mbined with oesophagomyotomy. These studies suggest that e risk of GORD after transthoracic short oesophagomyotomy certainly no greater than that after a combined procedure.

Critics of the short myotomy point out that it may be too ort, resulting in failure to relieve the obstruction caused by e non-relaxing sphincter. Five of the present patients had ersistent or recurrent dysphagia thought to be on this basis. emyotomy is possible under such circumstances, often with satisfactory result. Two of the present patients required bsequent extension of the myotomy, but only one of these as benefited. The other three patients were symptomatic but id not accept the recommendation of a second procedure.

The present data suggest that symptomatic improvement llowing transthoracic short oesophagomyotomy is maintained r up to 20 years, although the level of improvement may ecrease with time. The late development of reflux symptoms three patients and impaired gastric emptying in a further ree suggests that progressive disease in the body of the sophagus may be responsible. Inconsequential reflux may ecome important if the oesophagus becomes so atonic as to e unable to clear regurgitated acid. Similarly, oesophageal mptying, which at first may be satisfactory even with an peristaltic oesophagus, may become markedly delayed with e passage of time when the strength of the contractions in e body of the oesophagus becomes ineffectual. This hypothesis quires documentation manometrically, but it supports the iew expressed by Barrett[23] 28 years ago:

> 'As the oesophagus of a patient who has achalasia cannot be restored to physiological normality, it is probable that the late results of this disease are less satisfactory than early postoperative assessment suggests.'

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Pattern and surgical treatment of gastric cancer in Singapore

A personal series of 150 patients with gastric cancer operated on ov an 11-year period in Singapore is reviewed. Cancer occurred in th antrum and/or body of the stomach in 117 patients and in the cardi in 33. Gastric tumours were well or moderately differentiate adenocarcinoma in 50 patients and poorly differentiated or signet rin cell carcinoma in 100. Surgical resection was performed on 115 patient in whom it was palliative in 47. Attempted cure by R_2 radical resectio was performed in 68 patients: 14 with stage I, 12 with stage II and 4 with stage III disease. There was no operative death in these 68 patient. In 82 patients operated on more than 5 years ago, five patients wit carcinoma of the cardia and 28 with cancer of the gastric antrum and/ body underwent curative resection. There were 12 known 5-yea survivors among the latter 28 patients; 16 of the 28 had stage III diseas six of whom survived 5 years. These results compare favourably wit those of an earlier report from Singapore in which there were no 5-yea survivors. The improved results probably accrue from earlier diagnos and the current policy of radical resection.

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Recent studies indicate that gastric cancer occurs in different biological forms, that the patterns of the disease are changing, and that diagnostic and therapeutic strategies influence long-term results. These features could help explain the marked difference in results of treatment of gastric cancer in Japan and in the West, and may hold the key towards advances in the management of the disease[1].

In Singapore, as in the West and Japan, there has been a significant decline in the incidence of gastric cancer in recent years. Singapore has a rapidly developing Asian society under considerable Western influence. In an attempt to contribute towards a clearer global perspective of gastric cancer, a personal series is reviewed to determine the current pattern and results of treatment of the disease in Singapore.

Patients and methods

During an 11-year period (October 1979 to September 1990), the first 6 years at Singapore General Hospital and the later 5 at National University Hospital, 150 patients were operated on by the author for gastric adenocarcinoma. After surgery, patients were followed personally to assess and correct any nutritional problems and to detect recurrence of disease.

The clinical records of each patient were analysed to obtain the following information: race, age and sex; symptoms and physical signs at presentation; operative findings and pathology report of site of disease; histological grading and stage of disease by tumour node metastasis (TNM) classification[2]; operative procedure; operative morbidity and mortality, and crude survival. Operative mortality was defined as death within 30 days of surgery or after a longer period if death was directly related to surgery. Late deaths were due either to recurrent disease or unrelated causes in the absence of recurrence. In the cohort of patients operated on between 1979 and 1985, the minimum crude 5-year survival rate was recorded; no statistical adjustments were made for deaths unrelated to gastric cancer and for patients who defaulted the full period of 5-year follow-up.

Some data on 45 patients treated in the first 5 years have been included in previous reports[3,4].

Operative procedures in attempted curative resection (68 patients)

Subtotal gastrectomy (42 patients). Subtotal gastrectomy was performed for an antral tumour when a 5-cm resection margin could be achieved without total gastrectomy (*Figure 1*). The small gastr remnant (less than one-fifth of the stomach) was anastomosed to jejunal loop by a Billroth II procedure with a Hoffmeister valve an short afferent jejunal loop. The distal line of resection was through th first part of the duodenum, leaving just enough duodenum for sa closure. The gastrectomy included resection in continuity of the greate omentum, gastrocolic ligament and lesser omentum, thus excising a six groups of perigastric lymph nodes except those of the left cardi the left gastric and coeliac nodes were included in the resected specime by ligating the left gastric artery at its origin from the coeliac arter Enlarged nodes along the common hepatic artery, hepatoduoden ligament and splenic artery were dissected separately. The mesocolo and peritoneal covering of the pancreas were dissected in continuit with the stomach when they were adherent to the tumour or containe tumour nodules. Splenectomy was not routinely performed.

Total gastrectomy (14 patients). Total gastrectomy was performe for tumour involving the body or whole stomach (*Figure 2*). In additio to the lymph nodes excised during subtotal gastrectomy, the dissectio

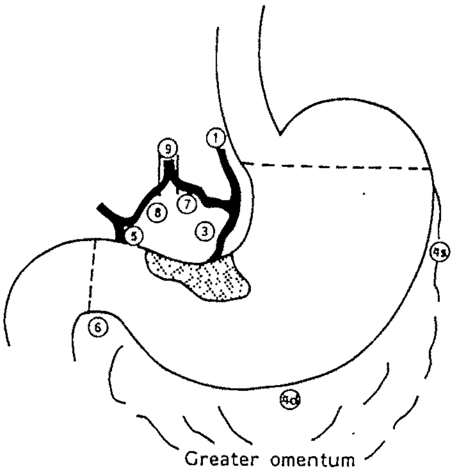

Figure 1 *Extent of resection in subtotal gastrectomy for tumours the antrum. Lymph nodes are numbered according to the recommendation of the Japanese Research Society for Gastric Cancer[5]: 1, right cardi node; 3, lesser curvature node; 4, nodes along short gastric, and righ and left gastroepiploic arteries; 5, suprapyloric node; 6, subpyloric node 7, lesser gastric artery node; 8, common hepatic artery node; and coeliac artery node*

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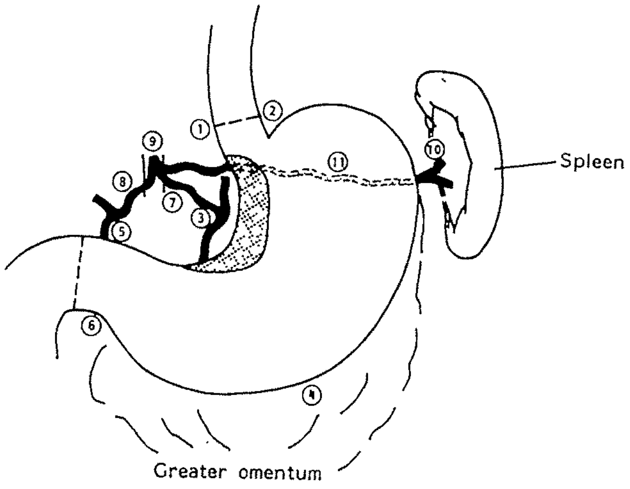
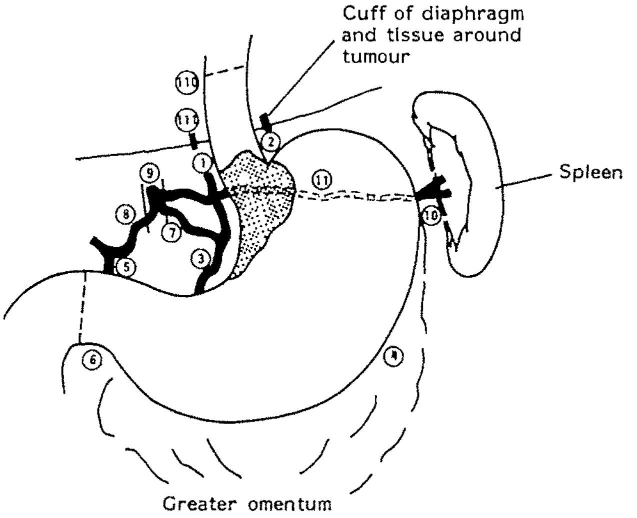


igure 2 *Extent of resection in total gastrectomy for tumours of the dy of the stomach, extending into the antrum, towards the cardia and wards both the cardia and antrum. Lymph nodes are numbered cording to the recommendations of the Japanese Research Society for astric Cancer*[5]. *In addition to those shown in* Figure 1 *these are: 2, left rdial node; 10, splenic hilum node; and 11, splenic artery node*



igure 3 *Extent of resection in oesophagogastrectomy for tumours of he cardia. Lymph nodes are numbered according to the recommendations f the Japanese Research Society for Gastric Cancer*[5]. *In addition to hose shown in* Figures 1 *and* 2 *these are: 110, lower thoracic araoesophageal node; and 111, diaphragmatic node*

n continuity included the left cardial nodes, the spleen and splenic ilar nodes. Reconstruction after total gastrectomy was by a 40-cm oux-en-Y oesophagojejunostomy, using hand suture with a single ayer of interrupted 3/0 silk or a circular stapling device.

Oesophagogastrectomy (*12 patients*). Oesophagogastrectomy was erformed for tumours of the cardia through a left thoracoabdominal ncision (*Figure 3*). The oesophagus was transected proximally at least 2 cm above the tumour. The distal line of resection was through the irst part of the duodenum in ten patients and between the upper and ower half of the stomach in two with small tumours. Oesophagectomy with total gastrectomy included removal of the spleen and dissection of group 1–11 lymph nodes. In addition, the lower thoracic paraoesophageal nodes and diaphragmatic nodes were excised and, if the tumour was adherent to the diaphragmatic hiatus, a cuff of diaphragm and tissue around the tumour was included in the excision. Reconstruction was by Roux-en-Y oesophagojejunostomy after oesophagectomy with total gastrectomy and by oesophagogastrostomy after oesophagectomy with partial gastrectomy.

Results

The gastric tumour occurred in the antrum, body or whole stomach in 117 patients and in the cardia, with extension into the gastric fundus and distal oesophagus, in 33.

There were three Malay, three Indian, one Irish and 143 Chinese patients; the male:female ratio was 1·4:1 for tumours of the antrum and body and 5·6:1 for those of the cardia. The age range was 27–88 years, with a mean of 60 years for tumours of the antrum and body and 65 years for those of the cardia.

The mean duration of the patients' history from the first symptoms to treatment was 9 months for tumours of the antrum and body and 8 months for those of the cardia. Clinical features of the patients are summarized in *Figures 4* and *5*. Patients with tumours of the cardia presented with dysphagia, with the exception of one with an early tumour who presented with dyspepsia. Patients with tumours of the antrum and body presented with epigastric pain as the most frequent symptom, with anaemia in half and a palpable epigastric mass in one-third of cases. Associated systemic disease was present more frequently in patients with carcinoma of the cardia compared with cancer of the antrum and body. This probably reflects the older age of presentation of the former patients.

Table 1 shows the operative management and the pTNM staging[2], based on clinical examination, laparotomy findings and histopathological examination of the resected specimen. Stage I or early gastric cancer was diagnosed in 14 patients. Advanced incurable stage IV disease occurred in 52 per cent of patients with tumours of the antrum and body, and in 63 per cent of those with tumours of the cardia.

Tumours were well or moderately differentiated adenocarcinoma in 50 patients and poorly differentiated or signet ring cell carcinoma in 100.

Trends in pattern of disease

Figure 6 shows the stage of disease at presentation for each 4-year period. Diagnosis of cancer of the antrum and/or body of the stomach at stage I increased from one patient for 1979–1982 to three patients for 1983–1986 and to nine for 1987–1990. The incidence of stage IV cancer of the antrum and/or body of the stomach, however, continued to be high, remaining at 50 per cent during the last two 4-year periods.

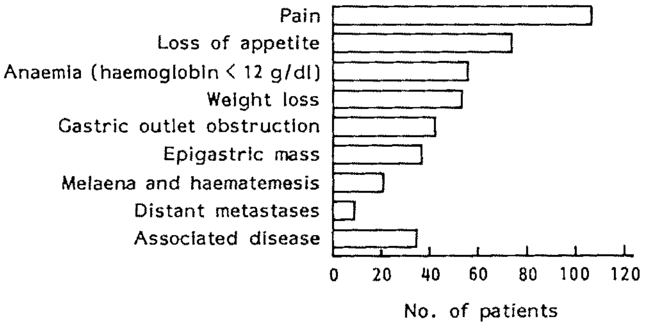


Figure 4 *Clinical features of 117 patients with tumours of the antrum and body of the stomach*

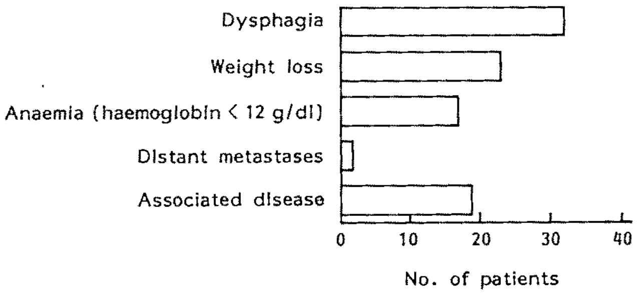
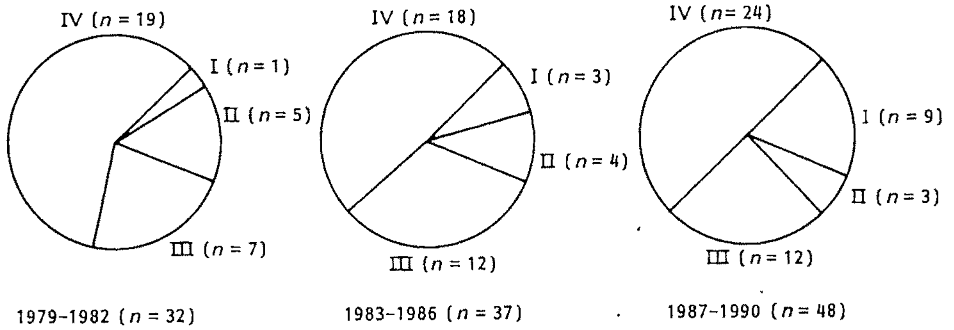


Figure 5 *Clinical features of 33 patients with tumours of the cardia*

Table 1 *Attempted curative R_2 resection in 68 patients with stage I–III gastric cancer*

Stage	Subtotal gastrectomy	Total gastrectomy	Oesophagectomy with partial gastrectomy	Oesophagectomy with total gastrectomy	To no
I	11	2	1	0	14
II	9	3	0	0	12
III	22	9	1	10	42
Total	42	14	2	10	68

Staging based on Kennedy[2]: stage I includes T_1N_0, T_1N_1 and T_2N_0; stage II includes T_1N_2, T_2N_1 and T_3N_0; stage III includes T_2N_2, T_3 T_4N_0, T_3N_2 and T_4N_1



1979–1982 (n = 32) 1983–1986 (n = 37) 1987–1990 (n = 48)

Figure 6 *Distribution by stage of 117 cases of gastric cancer of the antrum and/or body for each 4-year period*

Apart from one patient with stage I disease diagnosed in 1989, adenocarcinoma of the cardia was consistently diagnosed late, either at stage III (11 patients) or, more usually, at stage IV (21).

The proportion of patients with adenocarcinoma of the cardia remained constant at 22, 23 and 21 per cent for each of the respective 4-year periods.

Surgical treatment

Surgical resection was performed whenever technically possible and was achieved in 115 patients. In 68 of these an attempt at cure was made by R_2 resection[5]. In 47 patients surgery was non-curative as there was residual tumour at the resection margin, peritoneum or liver. It was not possible to resect tumour in 35 patients because of massive disease; palliative gastrojejunostomy or feeding jejunostomy was performed.

Operative morbidity and mortality

Attempted curative resection was performed on 68 patients (*Table 1*) with no operative death. However, two patients had anastomotic leakage: one after total gastrectomy and one after oesophagectomy with partial gastrectomy. Both patients recovered after parenteral nutrition, and drainage of subphrenic abscess and left empyema.

Palliative resection was performed on 47 patients, 20 undergoing partial gastrectomy, 11 total gastrectomy, four oesophagectomy with partial gastrectomy and 12 oesophagectomy with total gastrectomy. Postoperative deaths occurred in six patients: from anastomotic leakage (one), empyema (two), hepatorenal failure (two) and thrombocytopenic purpura with brain stem haemorrhage (one). Other major postoperative complications were pancreatic fistula (one patient) and empyema (two).

Table 2 *Minimum crude 5-year survival rate in 28 patients under curative surgery for cancer of the antrum and/or body in 1979–1*

Stage	No. of patients	Known 5-year survivors	Comments on other patient
I	3	2	One 65-year-old man died af years from respiratory fai with no evidence of recur
II	9	4	One patient died from recu cancer 4·7 years after sur One patient died at 3 years unknown cause Three patients were lost to follow-up
III	16	6	Seven patients died from recu cancer Three patients were lost to follow-up
Total	28	12	

Survival at 5 years

During the period 1979–1985, 82 patients were treated for carcinoma of the stomach and cardia. Curative resection was performed in 33 to give a curative resection rate of 40 per cent.

Of 64 patients with carcinoma of the antrum or body, curative resection was performed on 28. Results are shown in *Table 2*; no adjustment has been made for age, for death from unrelated causes and for patients who defaulted follow-up. Of the 28 patients who underwent curative surgery for canc the antrum and/or body, 12 are known to have surviv years; 16 of the 28 had stage III disease, six of whom 5-year survivors.

Of 18 patients with adenocarcinoma of the cardia tre between 1979 and 1985, five underwent curative resectio stage III disease. There were no known 5-year survivors: patient died from recurrent disease, three from unrelated ca (one at 4 years after surgery) and one was lost to follow The crude survival rate at 5 years for the 82 patients tre for gastric cancer at all sites during the period 1979–1985 15 per cent.

Discussion

Gastric carcinoma in Singapore occurs most commonly an Chinese. In the present series, 143 (95 per cent) of 150 pat were Chinese, although this race forms 75 per cent o population of Singapore. The Singapore Cancer Reg (1978–1982) shows overall annual age-standardized rat 31·6 and 14·6 per 100 000 male and female residents respecti

3 and 15·3 per 100 000 for Chinese men and women, 9·3 and per 100 000 for Malay men and women, and 15·6 and 16·5 100 000 for Indian men and women[6]. Gastric cancer in gapore Chinese is thus intermediate in incidence between very high annual age-standardized rates of 79·6 and 36·0 100 000 men and women in Japan (Miyagi, 1978–1981) d the 18·5 and 7·8 per 100 000 men and women in England d Wales (1979–1982)[7].

In recent years, as in the West and Japan, the incidence of tric cancer in Singapore has shown a decline; for 1968–1982 alling trend of 2·3 per cent per year for men and 1·5 per cent women has been recorded[6]. This is in contrast to the rkedly increasing incidence of colorectal carcinoma, which w exceeds that of gastric cancer in Singapore. The changing ttern of these two diseases may be related to a move from traditional Chinese diet (low in protein and fat, with salted getables, fish and rice) to a more Westernized high-fat h-protein diet.

The falling incidence of gastric cancer in the West and Japan s been caused by a decline in the number of antral tumours. contrast, the absolute incidence of carcinoma of the cardia s been reported to be rising[8]. Adenocarcinoma of the cardia ms an increasing proportion of the total number of cases of stric cancer, and in the present series constituted 22 per cent all cases. Adenocarcinoma of the cardia, as in other series, curred in slightly older patients (mean age 65 years) mpared with tumours of the antrum and body (mean age 60 ars) and showed a more marked male predominance ale:female ratio 5·6:1) compared with cancer of the antrum d body (sex ratio 1·4:1).

The results of treatment of gastric cancer vary. In a previous ngapore series of 112 cases[9] reported in 1973, there were no own 5-year survivors. The present series is encouraging in at 12 patients in a group of 28 who underwent curative surgery r cancer of the antrum and/or body survived at least 5 years, th an overall minimum crude 5-year survival rate of per cent.

This improvement in the results of treatment of gastric ncer in Singapore accrues in part from diagnosis at an earlier ge. Increasing affluence and improved medical care, cluding wider use of endoscopy for the investigation of spepsia, may have contributed to the earlier diagnosis. In lation to other parts of the world, the incidence of stage I stric cancer of 9 per cent and the 40 per cent curative resection te in the present series compare favourably with data from e much larger Birmingham, UK, series of a 1 per cent cidence of stage I disease and a 21 per cent curative resection te (stages I, II and III)[10], but fall well short of the 30 per cent cidence of early gastric cancer and 75 per cent curative section rate reported from Japan[5].

Although some progress has been made in the present series wards earlier diagnosis of tumours of the antrum and body, ncer of the cardia is diagnosed only at a late stage when sphagia is present. The continuing late presentation of stage I and IV disease and the poor prognosis of adenocarcinoma the cardia have also been experienced in other centres[11].

Apart from the stage of disease, the occurrence in varying oportions of the two Laurén histological types of cancer with eir different biological behaviour has been suggested to be portant in explaining differences in survival rates between pan and the West[12]. This view has, however, been questioned y the finding that, of the prognostic factors in gastric cancer[13], istological type had a relative risk factor of only 1·16. A recent aper from Japan[14] also reported that, as in the West, there is n increasing incidence of signet ring cell carcinoma.

A factor of greater importance in survival may be the extent f resection. Radical R_2 gastrectomy as practised empirically Japan is based on the rationale that the major cause of eatment failure in gastric surgery is local recurrence. This approach has been vindicated by superior results over 30 years and has some supporters in the West[15,16], although its wider acceptance may have to wait the results of controlled trials currently being undertaken there.

In the present series the author approximated R_2 resection and found that, as with some other series outside Japan, it can be performed safely; there were no operative deaths in 68 cases of attempted curative resection. Follow-up results have also been encouraging, with a crude minimum 5-year survival rate of 43 per cent.

Macroscopic diagnosis of nodal status is inaccurate. Even in early gastric cancer, metastasis to group 2 lymph nodes was found in 1·5 per cent of cases[17]. Routine radical resection for suspected stage I–III gastric cancer provides more accurate staging while at the same time maximizing the chance of complete resection of tumour.

In conclusion, the present findings support the more aggressive approach towards gastric carcinoma adopted in Japan. It would appear that, in surgery for gastric cancer, a complete and meticulous lymph node dissection can be performed safely, with improved prospects of cure in a disease notorious for its poor prognosis.

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Prognostic significance of histological type in gastric carcinoma with invasion confined to the stomach wall

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Survival was determined after resection for the two main histologic types of gastric carcinoma, intestinal (n = *223*) *and diffuse* (n = *170 in 393 patients with* pT_1 *or* pT_2 *tumours. Lymph node metastases we present in 94 patients. The 10-year survival rate was significantly low for patients with intestinal-type than for those with diffuse-ty carcinoma* (*72* versus *91 per cent,* P < *0·005*)*. In patients without nod involvement, the 10-year survival rate was still lower for those wi intestinal-type cancer* (*70* versus *94 per cent,* P < *0·01*)*. Recurrence carcinoma was more often by haematogenous dissemination in patien with intestinal-type cancer. Although the results of resection for* pT_1 *pT*$_2$ *gastric carcinoma can be acceptable, the introduction of adjuva therapy based on histological findings may be necessary for patien with the intestinal type of cancer to prevent haematogenous spread carcinoma to the liver.*

The present authors previously reported that the influence of the two main histological types of gastric carcinoma, intestinal and diffuse[1], on the survival rate for patients with gastric cancer varies according to the depth of invasion of the tumour into the gastric wall[2]. For patients with cancer confined to the stomach wall, the 5-year survival rate was lower for those with intestinal-type than for those with diffuse-type carcinoma. By contrast, in patients with cancer that invaded the serosa or adjacent tissues, the 5-year survival rate was higher for those with the intestinal type of carcinoma. The results of the present authors' survival analysis differed from those of studies performed in other countries, where a poorer prognosis has generally been reported for patients with diffuse-type carcinoma[3,4]. This may not, however, be the case when the serosa is tumour-free and nodal involvement was not taken into consideration in the previous study[2]. The present analysis was undertaken to include a larger number of patients and those with negative nodes.

Patients and methods

A total of 745 patients with carcinoma of the stomach underwent gastric resection during a period of 18 years (1 January 1974 to 31 December 1991) at this department. The resectability rate was 79·7 per cent. Of the 745 patients, 261 had a pT_1 tumour (invasion of the mucosa or submucosa but not of the muscularis propria) and 132 had a pT_2 lesion (invasion of the muscularis propria or subserosa)[5].

The histological type was classified as either intestinal or diffuse according to Laurén[1]. Of the 745 patients, 34 had synchronous multiple tumours, double early cancers were found in 17, triple early tumours were found in two, a combination of early and advanced cancer was found in 13, and double advanced tumours were found in two. In the 15 patients with at least one advanced tumour, the histological type was recorded for the lesion that had invaded the deeper layer. In the 19 patients with multiple early cancers, the histological type was recorded for the largest tumour. Mucinous carcinomas were found to have structural characteristics in common with either the intestinal or diffuse type, so they were classified according to structural features. One type, classified as intestinal, had distinct, usually large, glandular lumina that were dilated and separated by a profuse pool of mucus in which they floated. The other type had mucus masses that accumulated around isolated cells or loose clusters of cells; this was classified as diffuse type. There were no gastric tumours composed solely of squamous cell carcinoma as these lesions always contained glandular elements in or close to the mucosa. Adenosquamous or squamous cell carcinomas were found mostly in association with the intestinal-ty tumours. The histological type of all tumours was determined by t structure of the cancer in or close to the mucosa, not by the histologic feature that quantitatively predominated. This enabled classification all tumours in the present study.

The operative mortality rate, defined as death within 1 month operation, was 2·4 per cent (18 of 745), although there was no operati death in patients with pT_1 or pT_2 tumours. The operative procedu was the same for all patients if surgical treatment was performed wi curative intent. The cumulative crude survival rate was calculated the Kaplan–Meier method. Differences between survival rates we evaluated by the generalized Wilcoxon test and differences in t distribution of the samples by the χ^2 test.

Results

In the 745 patients who underwent resection, the diffuse ty of carcinoma was significantly more frequent in those wi tumours classed as pT_3 (invasion of the serosa without invasi of contiguous structures) or pT_4 (invasion of contiguo structures) than in those with pT_1 or pT_2 tumours ($\chi^2 = 18$ 2 d.f., $P < 0{\cdot}001$; *Table 1*). Of 393 patients with pT_1 or pT tumours, the 5-year survival rate was 93 per cent and the 10-ye survival rate 91 per cent for those with diffuse-type carcinom These survival rates exceeded those for patients wit intestinal-type cancer (86 and 72 per cent respectivel (*Figure 1*). Of patients with pT_1 or pT_2 tumours, lymph nod were not involved in 299 cases (76·1 per cent). *Figure 2* show survival related to histological type in patients in whom nod

Table 1 *Histological type and tumour stage in 745 patients wh underwent gastric resection*

	Histological type		
Stage of tumour	Intestinal	Diffuse	Tota
pT_1	144	117	261
pT_2	79	53	132
pT_3 or pT_4	145	207	352
Total	368	377	745

A total of 935 patients had gastric carcinoma (resectability ra 79·7 per cent)

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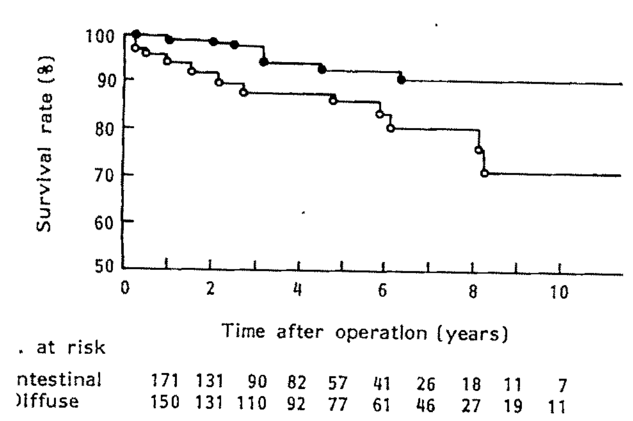
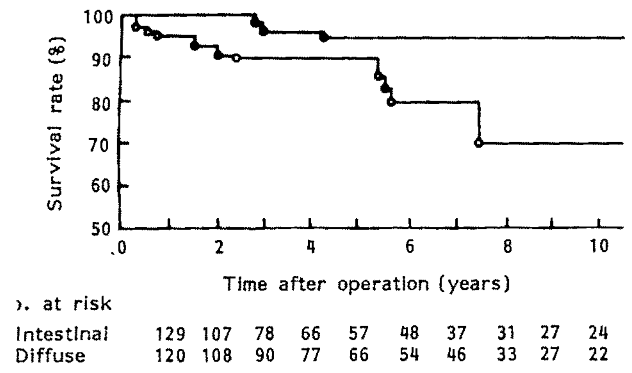
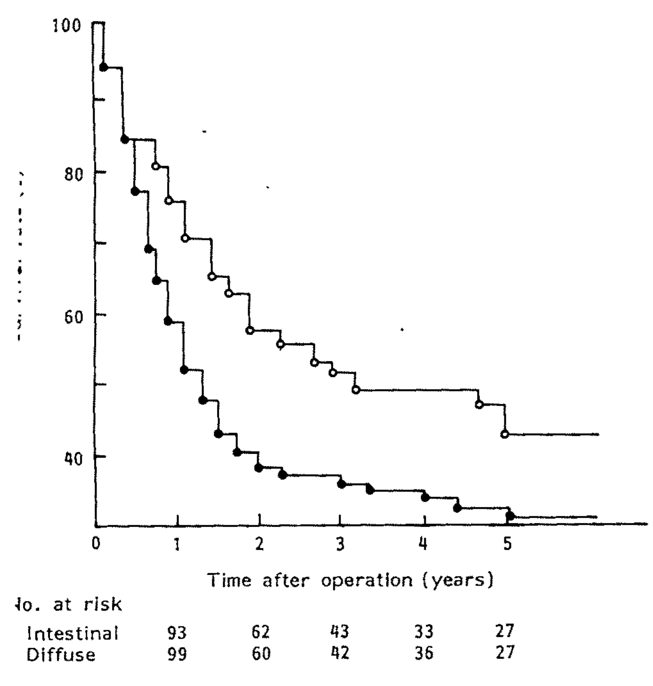


gure 1 *Survival rate according to histological type in patients with* $_1$ *or* pT_2 *gastric carcinoma.* ●, *Diffuse type* (n = *170*); o, *intestinal* e (n = *223*). P = *0·0042* (*generalized Wilcoxon test*)



igure 2 *Survival rate according to histological type in patients with* *de-negative* pT_1 *or* pT_2 *gastric carcinoma.* ●, *Diffuse type* (n = *132*); *intestinal type* (n = *167*). P = *0·0088* (*generalized Wilcoxon test*)



igure 3 *Survival rate according to histological type in patients with* T_3 *or* pT_4 *gastric carcinoma.* ●, *Diffuse type* (n = *207*); o, *intestinal* *ype* (n = *145*). P = *0·0017* (*generalized Wilcoxon test*)

Table 2 *Cause of death after gastric resection in patients with* pT_1 *or* pT_2 *tumours*

	Histological type	
	Intestinal	Diffuse
Cancer-related		
Haematogenous dissemination	19	2
Nodal recurrence	3	3
Peritoneal recurrence	1	7
Other		
Myocardial infarction	2	0
Renal insufficiency	2	0
Unknown	1	0
Total	28	12

were not involved. Survival rates at 5 and 10 years were higher in patients with the diffuse type than in those with the intestinal type of carcinoma (94 *versus* 90 per cent and 94 *versus* 70 per cent respectively). By contrast, in patients with pT_3 or pT_4 tumours the survival rate was higher for those with intestinal-type cancer (*Figure 3*).

Table 2 shows the cause of death for patients with pT_1 or pT_2 tumours. Of 28 patients with pT_1 or pT_2 intestinal-type carcinoma who died after supposedly curative operation, 23 succumbed after recurrence of cancer. Haematogenous dissemination accounted for 19 of these recurrences. The incidence of blood-borne metastases after supposedly curative surgery was significantly lower in patients with diffuse-type carcinoma (17 *versus* 83 per cent, $P < 0·01$). There was no cancer-related death or recurrence of carcinoma in patients with intramucosal tumours irrespective of histological type.

Discussion

It is currently considered that diffuse-type gastric carcinoma is a more advanced stage of disease than intestinal-type[6,7]. The high incidence of the former in more advanced disease seems to represent a histological transformation from the intestinal to the diffuse type related to the depth of invasion[8], from pT_1 to pT_4. This viewpoint is confirmed in the present study (*Table 1*). It is also widely believed that the diffuse type of gastric carcinoma has, in general, a less favourable prognosis[3,4]. The results of the present study suggest otherwise. For patients with pT_1 or pT_2 gastric tumours the prognosis for the diffuse type was better than for the intestinal type.

Lymph nodes were involved in 23·9 per cent of patients with pT_1 or pT_2 gastric cancer. These involved nodes can be completely removed by extended lymphadenectomy, which may be why the predominant cause of death in patients with intestinal-type gastric carcinoma is haematogenous dissemination (*Table 2*).

Blood-borne metastasis cannot be prevented exclusively by surgical procedures. Although the postoperative survival rate for patients with pT_1 or pT_2 gastric carcinoma is, in general, acceptable, additional therapy may be appropriate, based on the histological features of the tumour. For example, intraoperative administration of chemotherapeutic agents via the portal system to prevent metastasis to the liver could further improve survival of patients with intestinal-type carcinoma. However, since cancer-related death was not seen in patients with intramucosal carcinoma, any adjuvant chemotherapy seems to be unnecessary for such patients.

It is concluded that, in patients with gastric cancer confined to the stomach wall (pT_1 or pT_2), survival is better in those with a diffuse rather than an intestinal type of tumour. This contrasts with the generally accepted poorer prognosis of patients with advanced diffuse-type disease.

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Case report

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Spontaneous rupture of a normal portal vein causing severe retroperitoneal and intraperitoneal bleeding

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Spontaneous rupture of the portal vein is rare. A literature search revealed only two cases, both of which involved rupture of an abnormal vessel[1,2]. A unique case of spontaneous rupture of a normal portal vein is reported.

Case report

A 58-year-old woman presented with hypovolaemic shock and mild upper epigastric discomfort. She had had neither haematemesis nor melaena and there was no history of trauma or liver disease. The woman had suffered a single episode of mild periumbilical pain 6 weeks earlier. Abdominal examination revealed mild epigastric tenderness with no guarding. Rectal examination was normal. The patient was resuscitated and blood pressure was restored to normal. After a period of stability she developed abdominal distension and again became hypotensive. Computed axial tomography (CAT) showed a large volume of intraperitoneal blood. Laparotomy was performed.

At laparotomy the liver, spleen, kidneys, abdominal aorta, and gastrointestinal and urinary tracts were all normal. There was, however, a large haematoma in the free edge of the lesser omentum. The bleeding point was found to arise from the right side of the portal vein below its entrance into the liver. The haemorrhage was controlled by pressure on the portal vein proximal to the bleeding point, which was under-run with polypropylene sutures. The postoperative course was unremarkable.

Results of postoperative abdominal CAT and upper gastrointestinal endoscopy were normal. Doppler ultrasonography showed normal flow in the portal and hepatic veins. Superior mesenteric angiography wi portal venography revealed no abnormality. The portal vein was normal shape and calibre.

Discussion

This is the only spontaneous rupture of a normal portal vei to be reported, although two cases of rupture of an abnorm portal vein have previously been described. Barzilai an Kleckner[1] reported a case of persistent gastrointestinal bleedin resulting from rupture of a portal vein aneurysm into t extrahepatic biliary tree. In 1967, Thomas[2] described a patie in whom thrombosis resulted in rupture of the portal vei Portal vein aneurysms are themselves extremely rare: only 1 extrahepatic and 13 intrahepatic cases have been recorded Most appear to have arisen as developmental anomalies or a complication of portal hypertension. The reported incidence of portal vein aneurysm in patients with portal hypertension two in 300.

Haemorrhage of the portal vein is more commonly seen i patients with penetrating or blunt abdominal trauma Approximately 200 such cases have been described in the pas 30 years. The mortality rate in patients with this injury varie between 59 and 70 per cent[5]. Despite close questioning afte recovery, the present patient could not recall sustaining an form of abdominal injury before symptoms developed. N evidence of a pre-existing anatomical abnormality of the porta vein was found by CAT, Doppler ultrasonography o angiography. It may be speculated that the mild epigastric pai experienced 6 weeks before presentation was premonitory.

In view of this case we believe that spontaneous rupture o the normal portal vein may now take its place as the rares cause of intraperitoneal haemorrhage.

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Kinetic changes and experimental carcinogenesis after Billroth I and II gastrectomy

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To determine the risk of gastric remnant cancer according to the type of surgical reconstruction, the distal two-thirds of the glandular stomach was resected in male Wistar rats, followed by gastroduodenostomy (Billroth I anastomosis) or gastrojejunostomy (Billroth II anastomosis). No carcinogens were given and the animals were killed 50 weeks after operation. No cancers developed in 22 rats undergoing Billroth I gastrectomy, but five of 24 with Billroth II anastomosis had adenocarcinoma ($P < 0{\cdot}05$)*. All carcinomas were confined to the stoma. Animals with Billroth II anastomosis had a more advanced grade of mucosal atrophy at the stoma, with a higher incidence of cystic dilatation, submucosal adenocystic proliferation and pseudopyloric metaplasia* ($P < 0{\cdot}05$)*. Cell kinetics in the stomal mucosa after Billroth II gastrectomy showed an increased cell count in the proliferative zone, longer duration of S phase and increased cell cycle time* ($P < 0{\cdot}05$)*. These results suggest that Billroth II gastrectomy carries a greater risk of cancer than the Billroth I procedure.*

fter distal partial gastrectomy, reconstruction is generally erformed by a gastroduodenostomy (Billroth I) or gastrojunostomy (Billroth II) anastomosis. The reported risk of ancer developing in the gastric remnant after each type of nastomosis has varied between studies. Some workers have ported an increased risk of stump cancer following Billroth gastrectomy[1–4]. Others have described a risk similar to that ollowing Billroth I anastomosis[5–10]. This discrepancy may ave been due to differences between groups in factors such as x, age, number of patients, length of follow-up, pathology of e original disease and the detection rate of cancer in clinical tudies. In addition, it remains unresolved what type of gastric ilieu is associated with the development of cancer.

Several authors have shown that rats submitted to an peration that allows reflux of large volumes of duodenal juice ill subsequently develop cancer in the gastric remnant without he administration of a carcinogen[11–14]. No studies have ompared carcinogenesis in the gastric stump after Billroth I nd II anastomoses. The aims of this study were to evaluate ifferences in tumour yield, morphology and cell kinetics in the ucosa of the residual stomach following distal gastrectomy rats with Billroth I or II anastomosis without the application f a carcinogen.

Materials and methods

nimals

Male Wistar rats weighing 200–250 g were used. Animals were housed n wire grid cages under controlled conditions at a temperature of 22°C nd a humidity of 55 per cent with a 12-h light–dark cycle. They were ed CRF-1 solid chow (Charles River, Yokohama, Japan) and tap vater *ad libitum*.

urgical technique

Animals were fasted for 36 h, after which laparotomy was performed nder general anaesthesia with intraperitoneal injection of pentobarbital 25 mg per kg body-weight) and ether inhalation. Removal of the distal wo-thirds of the glandular stomach was followed by either Billroth I r II anastomosis as shown in *Figure 1*. Anastomosis was performed sing 7/0 silk sutures. Rats were allowed to drink immediately after peration and to eat 48 h later. The animals were weighed every 5 veeks during the experiment. Those that survived for 50 weeks after peration were killed by exsanguination under anaesthesia. Twenty-two nimals underwent Billroth I and 24 Billroth II gastrectomy.

Pathology

The gastric remnants were removed, incised along the greater curvature and washed with 10 per cent formalin. Each stomach was pinned out with the mucosal side uppermost and the mucosal surface was observed macroscopically. The preparations were then fixed in 10 per cent formalin for at least 3 days and tissue samples cut at 3-mm intervals into step sections perpendicular to the line of anastomosis. Specimens were embedded in paraffin and the block cut into thin sections ($6\ \mu m$) and stained with haematoxylin and eosin, periodic acid–Schiff or pH 2·5 alcian blue. Mucosal thickness was measured only in the longitudinally sectioned gastric pits and was expressed as the mean value for each animal in ten glands examined microscopically. Definitions of lesions included adenocarcinoma, adenoma, cystic dilatation, submucosal adenocystic proliferation and pseudopyloric metaplasia. Adenomatous growth with both atypia and invasion was classified as adenocarcinoma; other adenomatous growths were defined as adenoma. Cystic formation of glands accompanying elongated gastric pits and dilated tubules was defined as cystic dilatation, and adenocystic proliferation observed under the muscularis mucosa classified as submucosal adenocystic proliferation. Pseudopyloric metaplasia was characterized by the oxyntic glands resembling pyloric glands.

Cell kinetics

Cell kinetics were analysed only in the gastric pits near the stoma, every third sample of the serially sectioned material being surveyed.

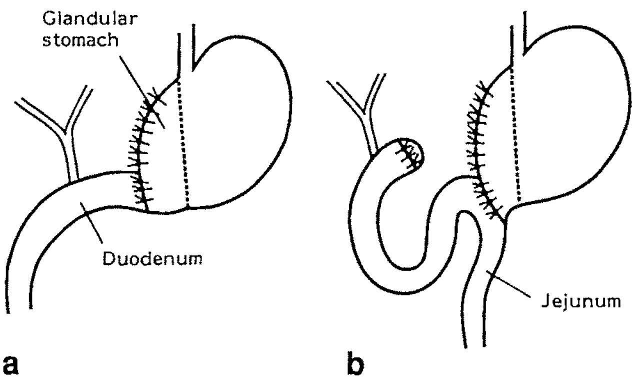

Figure 1 *Surgical procedures. The distal two-thirds of the glandular stomach was resected, with* **a** *Billroth I or* **b** *Billroth II reconstruction*

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Proliferative parameters were assessed in a minimum of ten gastric pits and were expressed as the mean value for each animal. In 17 rats undergoing Billroth I gastrectomy and 20 with Billroth II anastomoses, the single-labelling method was performed using 5-bromo-2′-deoxyuridine (BrdU). The cell count in the proliferative zone was calculated as the number between labelled cells in the uppermost layer and the bottom of the gastric pits. The S phase labelling index was estimated as the ratio of the number of labelled cells to the number of cells in the proliferative zone. In addition, the duration of S phase and the cell cycle time were determined by a double-labelling method, using the time lag in labelling with BrdU and 5-iodo-2′-deoxyuridine (IdU) in five rats undergoing Billroth I and four Billroth II gastrectomy.

Single-labelling method. At 1 h before the rats were killed, 20 mg per kg body-weight BrdU was injected intraperitoneally. Cells labelled with BrdU were identified by an avidin–biotin–peroxidase complex (ABC) method using an anti-BrdU antibody (Becton–Dickinson Monoclonal Center, Mountain View, California, USA) as the primary antibody. After being deparaffinized, sections were rinsed in 2 mol/l hydrochloric acid for 30 min, 0·1 mol/l sodium tetraborate for 10 min, and phosphate-buffered saline (PBS) and 0·05 per cent protease solution for 10 min. After immersion in methanol containing 0·3 per cent hydrogen peroxide to block endogenous peroxidase, sections were washed with PBS. They were then covered with a 1:50 normal goat serum for 30 min and with a 1:50 dilution of anti-BrdU antibody for 2 h. Sections were rinsed in PBS and covered with a 1:50 dilution of biotinylated goat antimouse immunoglobulin (Ig) G for 1 h. After rinsing in PBS, sections were covered with ABC solution (Vectastain ABC kit; Vector Laboratories, Burlingame, California, USA) for 30 min and incubated for 10 min in 0·5 mg/ml 3,3′-diaminobenzidine tetrahydrochloride. The sections were counterstained with haematoxylin; BrdU stained brown.

Double-labelling method. The rats were injected intraperitoneally with 20 mg per kg body-weight IdU and with the same amount of BrdU after 3 h. Animals were killed 1 h later. Sections were stained by a double-labelling technique using the ABC method for Br-3 and an alkaline phosphatase–anti-alkaline phosphatase (APAAP) method for anti-BrdU[15]. Br-3 (Caltag Laboratories, San Francisco, California, USA) is a monoclonal antibody recognizing only BrdU, whereas the anti-BrdU antibody reacts with both BrdU and IdU.

The ABC technique for Br-3 was carried out using the same procedure as in the single-labelling method. Sections were then treated with 5 per cent acetic acid overnight to inactivate Br-3, rinsed with 0·05 mol/l Tris-buffered saline (TBS) and incubated for 2 h in a 1:50 dilution of anti-BrdU antibody. After a rinse with TBS and treatment with 1:50 rabbit antimouse IgG for 1 h, sections were rinsed with TBS and covered with 1:10 APAAP complex for 30 min. After rinsing in TBS, the substrate solution was prepared by dissolving 2 mg naphthol-AS/MX phosphate in 0·2 ml dimethylsulphoxide and adding 10 ml 0·1 mol/l Tris-HCl, pH 8·6. Levamisol (0·25 mg) was then added, and just before staining 10 mg fast blue BB salt was dissolved. Sections were treated with the substrate solution for 30 min, then counterstained with methyl green. IdU alone stained blue; IdU and BrdU together stained as brown reaction products.

The S phase duration and cell cycle time were calculated using the following equations:

$$\text{Duration of S phase (h)} = 3 \times \frac{\text{number of cells stained with BrdU and/or IdU}}{\text{number of cells stained with IdU alone}}$$

$$\text{Cell cycle time} = 100 \times \frac{\text{duration of S phase}}{\text{BrdU labelling index}}$$

Serum gastrin levels

The level of serum gastrin was measured by the radioimmunoassay polyethylene glycol method[16], using serum separated from blood collected from the inferior vena cava.

Statistical analysis

Differences in percentages were analysed by the χ^2 test with Yates' correction for small numbers. Means were compared by Student's t test for paired samples. $P < 0{\cdot}05$ was considered significant.

Results

There was no difference in the increase in body-weight between the two experimental groups.

Pathology (Table 1)

Tumours developed in six rats receiving Billroth II gastrecto but in none of those with Billroth I anastomosis ($P < 0{\cdot}0$ All lesions were located near the stoma (*Figure 2*). Histologi examination revealed the tumours to be adenocarcino and/or adenoma: carcinoma developed in five rats (21 per ce and adenoma in three (12 per cent) in the Billroth II grou Adenocarcinomas were mucinous in three rats and tubular two. Neither lymph node nor distant metastases were foun

There was a significant difference in the incidence adenocarcinoma between the groups ($P < 0{\cdot}05$). The incide of cystic dilatation, submucosal adenocystic proliferation a pseudopyloric metaplasia was also higher in rats submitted Billroth II gastrectomy. Again, these histological lesions w detected only in the stomal region. Intestinal metaplasia rare. In the stomal area, the mean(s.d.) depth of whole muco the oxyntic gland layer and foveolar epithelium was 0·44(0·0 0·31(0·08) and 0·13(0·06) mm respectively after Billroth gastrectomy, as opposed to 0·40(0·14), 0·20(0·15) a 0·20(0·10) mm for Billroth II anastomosis. The oxyntic gla layer was significantly thinner after the Billroth II procedu whereas the foveolar epithelium was significantly thic ($P < 0{\cdot}05$). The oxyntic mucosa in the stomach away from stoma showed mild atrophy in both sets of rats, but difference in the grade of atrophy was observed between grou

Cell kinetics (Table 2)

The mean cell count in the proliferative zone near the sto in rats undergoing Billroth II gastrectomy was twice that those having the Billroth I operation, although the me

Table 1 *Incidence of tumours and histological changes in the gas remnant*

	Gastrectomy	
	Billroth I ($n = 22$)	Billrot ($n = 2$
Tumour	0 (0)	6 (25)
Adenocarcinoma		
Mucinous	0 (0)	3 (12)
Tubular	0 (0)	2 (8)
Total	0 (0)	5 (21)
Adenoma	0 (0)	3* (12)
Cystic dilatation	7 (32)	19 (79)
Submucosal adenocystic proliferation	2 (9)	12 (50)
Pseudopyloric metaplasia	6 (27)	22 (92)

Values in parentheses are percentages. *Adenocarcinoma associated with adenoma in two rats. †$P < 0{\cdot}05$ (Yates' χ^2 test)

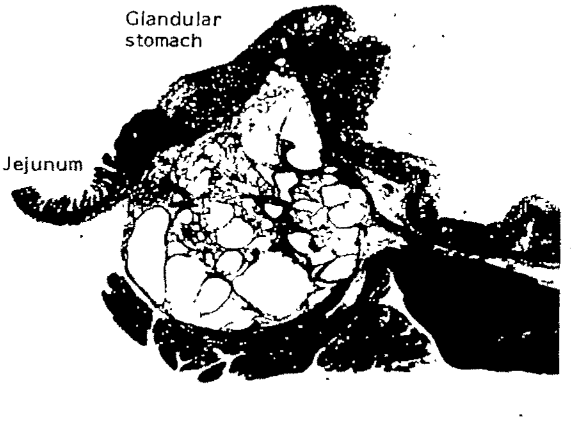

Figure 2 *Loupe image of cancer observed at the stoma of the gas remnant after Billroth II gastrectomy*

ble 2 *Cell count, labelling index, S phase duration and cell cycle te in the proliferative zone near the stoma of the gastric remnant*

	Gastrectomy	
	Billroth I (*n* = 22)	Billroth II (*n* = 24)
ll count	10·6(3·7)	21·8(12·7)*
belling index (%)	39·6(11·9)	33·8(8·9)
phase duration (h)	8·3(2·2)	12·0(2·1)*
ll cycle time (h)	20·9(5·6)	35·5(6·3)*

lues are mean(s.d.). S phase duration and cell cycle time were sessed in five rats in the Billroth I group and four in the Billroth II oup. *$P < 0·05$ (Student's paired *t* test)

belling index was similar. These results indicate an elongated oliferative zone after Billroth II gastrectomy. The mean S ase duration and cell cycle time were longer in the Billroth group.

erum gastrin levels

he mean(s.d.) serum gastrin level was 189(47) pg/ml in rats dergoing Billroth I gastrectomy and 176(96) pg/ml after illroth II anastomosis. There was no significant difference etween these values.

iscussion

pontaneous gastric carcinogenesis is rare in experimental rats. ullock and Curtis[17] found that, in a collective series of 33 000 ts examined at post mortem, only one had gastric adeno-rcinoma. Ratcliffe[18] reported 273 spontaneous tumours ccurring in rats, but no gastric lesions. A previous experiment y the present authors[19] showed that rats with a gastrotomy id not develop a single gastric tumour within 50 weeks of peration. In the present experiment, no tumours were found fter Billroth I anastomosis, but gastric adenocarcinoma eveloped following Billroth II reconstruction. Thus, modifiation of the environment following Billroth II resection induces rcinogenesis in the gastric remnant.

There are two kinds of disturbed gastric physiology related o carcinogenesis in the Billroth II stomach: a lower level of irculating gastrin and a higher degree of duodenogastric reflux. he removal of the pyloric antrum decreases the amount of irculating gastrin. After Billroth II anastomosis, food never omes into contact with the duodenum, hence there is less timulation of duodenal mucosal gastrin, and circulating gastrin evels might therefore decrease more markedly. Decreased astrin concentrations result in atrophy of the oxyntic ucosa[20,21], which may predispose to gastric carcinoma. In ddition, gastrin *per se* might affect the growth of gastric umours[22]. Nevertheless, no difference could be found in the egree of atrophy in regions other than the stomal area in the resent study. There was also no difference in fasting gastrin evels between the two groups, suggesting that a lack of uodenal gastrin secretion in the rats with Billroth II gastrectomy did not play a major role in carcinogenesis or ucosal changes of the gastric remnant.

On the other hand, it is well established that duodenal ecretion is a risk factor for gastric carcinogenesis. Dahm *et l.*[23] reported that rats with Billroth II gastrectomy have a igher incidence of gastric stump cancer induced by V-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) than those vith Roux-en-Y reconstruction. Langhans *et al.*[11] showed a positive correlation between the degree of duodenogastric reflux nd the incidence of cancer in the operated rat stomach. The resent study revealed that carcinoma was confined to the egion of the stoma, which was constantly exposed to a large quantity of duodenal contents at a high concentration. Thus eflux of duodenal contents is the most likely cause for the development of cancer in the gastric remnant. Adenocarcinoma often accompanied other histological alterations in this rat model, including atrophy of oxyntic glands, foveolar hyperplasia, cystic dilatation, submucosal adenocystic proliferation, pseudopyloric metaplasia and adenoma. Such lesions are almost identical to those observed in the human gastric remnant[24,25], although intestinal metaplasia was rare in rats but is common in man. Similar observations were reported by Mason[14].

It is well known that distal gastrectomy increases epithelial cell proliferation in the remaining stomach[26–29]. Langhans *et al.*[30] found an increased labelling index after Billroth II compared with Billroth I anastomosis in rats. Houghton *et al.*[31] showed greater cell proliferation following Pólya partial gastrectomy than after Roux-en-Y biliary division in rats given MNNG. Taylor *et al.*[32] found that rats subjected to gastrojejunostomy have an increased labelling index in the adjacent foveolae and a subsequent increase in tumour yield. Although the labelling index was unchanged in the present study, the proliferative zone was elongated around the Billroth II stoma. Increased proliferative activity may predispose to carcinogenesis in skin, colon and pancreas[33–37]. Since increased gastric cell proliferation has a close correlation with the degree of atrophic gastritis[38–41], its presence following Billroth II gastrectomy may reflect gastric atrophy caused by the direct action of duodenal secretion.

The duration of S phase and cell cycle time have seldom been measured in the gastric remnant, but in the present experiments they were significantly longer after Billroth II than after Billroth I gastrectomy. In human skin and colorectum, S phase duration is longer in the tumour than in the adjacent tissue[42–44], and Bleiberg *et al.*[44] have suggested that a prolonged S phase is associated with carcinogenesis. Premalignant lesions in the skin that evolve into basal cell carcinoma show a prolonged S phase[45], suggesting impairment of DNA function.

Although no stump cancers were seen in rats with a Billroth I anastomosis, Meyer *et al.*[46] found a few tumours under these experimental circumstances (in five of 75 animals at 104 weeks). Unfortunately, the present study had no control group without gastrectomy, so cell kinetic changes after this procedure could not be evaluated. Nevertheless, Meyer *et al.*[29] did find glandular distortion and increased labelling near the Billroth I anastomosis, suggesting that this procedure might eventually also be carcinogenic.

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Intraoperative enteroscopy in Crohn's disease

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Intraoperative small bowel endoscopy was performed on 33 occasions in 31 patients with Crohn's disease. The extent of mucosal inflammation was compared with that of changes in the external bowel wall: serositis, fat-wrapping and mural thickening. The influence of endoscopic findings on surgical management was evaluated. Mucosal inflammation was generally more extensive than serositis ($P < 0.01$)*, but less so than mural thickening* ($P < 0.001$)*. The extent of fat-wrapping did not differ from that of mucositis. Of 23 patients undergoing reoperation or with fistula or abscess, however, eight had serositis and/or fat-wrapping in bowel segments without mucosal inflammation. Endoscopic findings influenced surgical decisions on 20 of the 33 occasions, limiting planned resection in 14, identifying strictures for repair in one, and deciding against resection in two cases and for extended resection in three. These results suggest that external inflammatory changes are unreliable guides to the extent of intestinal mucositis and requirements for resection in Crohn's disease. By visualizing the mucosa, intraoperative enteroscopy can provide information for more precise surgery, thereby limiting resection.*

urgery remains important in the management of Crohn's isease, although most surgeons agree that as much bowel as ossible should be preserved and that only grossly affected reas should be resected[1,2]. Conservative operations such as rictureplasty have been recommended for extensive Crohn's isease of the small bowel[3,4]. The surgical strategy is governed rimarily by information obtained from radiological investigation, preoperative endoscopy and peroperative inspection of he bowel and resection margins.

The aetiology and pathophysiological basis of Crohn's isease are still obscure. Intestinal vasculitis was recently uggested[5], but many previous studies implicated aphthous lcers as the primary lesion and serosal changes as econdary[6-9]. Information on the appearance of the intestinal ucosa should therefore be useful for decisions concerning esection. The relationship between gross serosal and gross ucosal inflammation in Crohn's disease has not been dequately studied. Intraoperative intestinal endoscopy provides n excellent means of assessing mucosal disease. The technique as been used to identify intestinal bleeding[10], but no evaluation as been performed of its utility in Crohn's disease.

The relationship between external intestinal inflammation f the small bowel and the appearance of the mucosal lining t intraoperative endoscopy in Crohn's disease was investigated. xperience from 33 consecutive operations is presented and the nfluence of intraoperative endoscopic findings on surgical anagement discussed.

atients and methods

n a 30-month period (September 1988 to March 1991), 37 consecutive atients with small bowel Crohn's disease underwent 39 laparotomies. ntraoperative endoscopy was performed on all but six occasions, two hen no trained endoscopist was available and four emergency rocedures for intestinal obstruction. The study included 19 male and 2 female patients aged 14–71 (median 33) years who underwent 33 perations, all with predominantly small bowel disease. Preoperative iagnosis was based on endoscopy[11], radiographic findings[12] and, in atients with previous surgical treatment, Morson's morphological riteria[13]. The indications for surgery were high activity of the disease efractory to medical treatment in 25 cases, fistula or abscess in seven nd retarded growth in one. Eighteen operations were primary resection nd 15 secondary resection. Patients were also grouped according to he presence of fistula or abscess at laparotomy and whether or not they had received long-term anti-inflammatory treatment, defined as administration of steroids, 5-aminosalicylic acid or azathioprine for more than 3 months.

Preparation of the bowel in the early part of the study included liquid diet for 2 days, oral laxative and enema. More recently, an osmotic intestinal washout was achieved with 4 litres polyethylene glycol solution (Laxabon; Tika, Lund, Sweden). Antibiotic prophylaxis with doxycycline or cefuroxime in combination with metronidazole was routinely given for 2 days.

Abdominal exploration

The bowel was inspected for external changes. The extent of the features listed in *Table 1* was determined by two examiners (K.S., G.O.); the limits were marked with sutures on the serosal wall and the length of involved bowel measured.

Intraoperative endoscopy

All endoscopies were performed by two examiners (K.S., G.O.), one guiding the instrument in the abdomen and the other examining the mucosa. An Olympus C10L colonoscope (Axel Johnson, Solna, Sweden) was used. The endoscope, in a sterile plastic cover, was introduced into the intestine through a small incision in a segment with gross external inflammation. The bowel was intubated by a combination of pull-through and telescoping the gut over the endoscope. Air was insufflated to facilitate viewing, with proximal spread of the air controlled by two fingers placed across the intestine to prevent generalized bowel distension. Endoscopic features of inflammation were used that had previously been shown to be reproducible between observers (*Table 1*)[14]. The limits of each endoscopic feature were identified, marked with sutures on the serosal surface, and the extent measured. The 33 intraoperative endoscopies

Table 1 *Indicators of intestinal inflammation at exterior inspection and intraoperative intestinal endoscopy*

- Exterior inspection
  - Palpable mural thickening (double thickness or more compared with normal bowel)
  - Fat-wrapping (fat creeping up the bowel wall)
  - Serositis (erythema with 'corkscrew' appearance of serosal vessels)
- Intraoperative enteroscopy
  - Aphthae (clear vesicles with red halo on otherwise normal mucosa)
  - Superficial ulcers
  - Deep ulcers (margins undermined)
  - Cobblestone formation
  - Stricture (intestinal lumen <15 mm)

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comprised 28 ileojejunoscopies with examination of 30–500 (median 100) cm of intestine and five ileocolonoscopies studying 90–330 (median 180) cm. The time required for the endoscopic procedure was 15–35 (median 20) min.

Surgical strategy

Traditional criteria for the extent of intestinal resection were formerly adopted. Involvement by any of the exterior features (serosal inflammation, fat-wrapping or palpable mural thickening) was used as an indication of macroscopically diseased intestine[15–17]. In the present series, the supplementary endoscopic information was also used to guide the choice of operation and, when the extent of mucosal inflammation and exterior features differed, the former was used to determine the choice of operation and extent of resection. If disease was confined to the distal ileum, all intestine with continuous inflammation was resected. When the small bowel was extensively involved, limited resection or strictureplasty was performed.

Statistical analysis

Values are given as median (range). The two-tailed paired Wilcoxon test was used.

Ethics

The study was approved by the ethical committee of the Faculty of Health Sciences at Linköping University and conformed with the Helsinki Declaration.

Results

Relationship of mucositis to external inflammation

Inflamed segments of small bowel were classified as main lesions or skip lesions; these were analysed separately.

The relationship between the extent of endoscopicall visualized mucosal inflammation in main lesions and that features seen on the bowel wall is shown in *Table 2*. Compare with mucosal inflammation, serositis was less extensive i 76 per cent of cases ($P < 0{\cdot}01$), while fat-wrapping was le extensive in 48 per cent and equal in 30 per cent ($P > 0{\cdot}05$ Mural thickening was more extensive in 67 per ce ($P < 0{\cdot}001$). The median (range) length of mucositis was 2 (0–100) cm, mural thickening 35 (0–129) cm, fat-wrapping 2 (0–128) cm and serositis 20 (0–80) cm.

Grouping of patients according to previous treatment or th presence of local sepsis (*Table 3*) showed that all five in who the extent of serositis exceeded that of mucosal inflammatio had previously undergone bowel resection and four current had fistula or abscess. Two of the three patients with equal extensive serosal and mucosal inflammation and six of the seve in whom the extent of fat-wrapping exceeded that of mucosit had undergone previous resection and/or currently had fistul or abscess. Long-term preoperative medication had no cle effect in these comparisons.

The association between various degrees of extern involvement and mucosal inflammation in main lesions of sma bowel is summarized in *Table 4*. Serositis combined wit fat-wrapping and mural thickening was associated with dee ulcers and cobblestoning in 96 per cent of cases and also wit stricture in 46 per cent. When only fat-wrapping and mura thickening were present, deep or superficial mucosal ulcers we found in 86 per cent of cases, but there was no cobblestonin or stenosis. Mural thickening as the only external change wa

Table 2 *Relationship between extent of external features of intestinal inflammation and that of endoscopically determined mucosal inflammation small bowel Crohn's disease*

	Extent of mural thickening *versus* mucositis		Extent of fat-wrapping *versus* mucositis		Extent of serositis *versus* mucositis	
	No. of operations	Median (range) difference (cm)	No. of operations	Median (range) difference (cm)	No. of operations	Median (range difference (cm)
Less	4	9 (1–17)	16	6 (1–41)	25	9 (1–50)
Equal	7	—	10	—	3	—
More	22	14 (2–95)	7	10 (2–35)	5	10 (5–50)

Table 3 *Extent of fat-wrapping and serositis in relation to endoscopically determined mucosal inflammation in small bowel Crohn's disease, accordin to repeat operation, local sepsis and medication*

	No. of operations	Extent of fat-wrapping *versus* mucositis			Extent of serositis *versus* mucositis		
		Less	Equal	More	Less	Equal	Mor
Primary resection	18	10	6	2	17	1	0
Repeat operation	15	6	4	5	8	2	5
Fistula or abscess							
Present	14	3	7	4	8	2	4
Absent	19	13	3	3	17	1	1
Long-term anti-inflammatory medication							
Present	18	8	5	5	15	1	2
Absent	15	8	5	2	10	2	3

Table 4 *Mucosal inflammation in small bowel segments with various external appearances*

	Endoscopic findings				
External findings	Normal mucosa	Superficial ulcers	Deep ulcers	Cobblestoning	Stricture
Serositis, fat-wrapping and mural thickening ($n = 28$)	1	0	27	27	13
Fat-wrapping and mural thickening ($n = 28$)	4	10	14	0	0
Mural thickening alone ($n = 22$)	10	10	2	0	0

able 5 *Influence of intraoperative endoscopic findings on extent of surgery in 31 patients with small bowel Crohn's disease undergoing 33 operations*

peration	Influence of endoscopic findings*	Median (range) length of small bowel (cm)
ocolic resection ($n = 19$)	Reduced ileocolic resection ($n = 6$)	30 (7–70)
	Extended ileocolic resection ($n = 3$)	5 (5–13)
	Reduced ileocolic resection and cancelled small bowel resection ($n = 2$)	12 (5–18)
ocolic resection and wedge resection of fistula to small bowel ($n = 4$)	Reduced ileocolic resection ($n = 3$)	6 (5–12)
ocolic resection and wedge resection of fistula to colon ($n = 3$)	Reduced ileocolic resection ($n = 1$)	14
ocolic resection and strictureplasty ($n = 1$)	Seven strictures identified for repair, one non-stricture lesion left *in situ* ($n = 1$)	—
all bowel resection ($n = 4$)	Reduced resection ($n = 2$)	25 (10–40)
ploratory laparotomy ($n = 2$)	Cancelled ileocolic resection ($n = 1$)	5
	Cancelled small bowel resection ($n = 1$)	50

alues in parentheses are numbers of operations influenced by findings at endoscopy

lated mainly to normal mucosa (46 per cent) or superficial ceration (46 per cent).

Of the 23 patients with previous small bowel resection d/or current fistula or abscess (nine previously operated on, ght with fistula or abscess, six in both categories), eight had owel segments with serositis and/or fat-wrapping but no ncomitant mucosal inflammation. Seven patients had gments with mural thickening but without mucositis.

External examination showed skip lesions of the small bowel nine patients. Concomitant mucositis was present in two ses. One of these two had eight skip lesions with deep mucosal lcers, seven of which also had a stricture <10 mm in length. he second patient had four skip lesions, three with and one ithout concomitant mucositis, and an intra-abdominal bscess. Two of the seven patients with skip lesions but no orresponding mucosal inflammation underwent further rgery. Fistula was present in five cases.

In eight patients, scattered aphthae or small superficial ulcers ere found in otherwise normal intestine far from the main sions.

nfluence of intraoperative endoscopy on extent of resection

ntraoperative endoscopy yielded information that influenced urgical decisions on 20 occasions (*Table 5*). In 14 cases the reviously planned extent of resection was reduced, in three it vas increased, and in two repeat resections were cancelled. The eason for exploration in one of the last two patients was ersistent abdominal pain and suspected recurrent inflammation, ut intraoperative endoscopy showed only two small reanastomotic ulcers in the ileum. The other patient had bdominal pain and a fistula of the abdominal wall. Although 50-cm length of small bowel showed serositis at exploration, o fistula connection with the intestine was found and at ntraoperative endoscopy the mucosa was normal.

The seven strictures in the patient with eight skip lesions vere identified endoscopically for repair. In four patients with kip lesions but normal corresponding mucosa, endoscopy esulted in cancellation of multiple resections. In seven patients ndergoing ileocolic resection, wedge excision of a fistula to ealthy proximal small or large bowel was performed. Intraperative endoscopy confirmed the clinical judgement that the vedge resections were performed in bowel free from primary nflammation and involved only by a fistula connection.

Endoscopic findings influenced the surgical procedure in 20 f 33 operations. In addition, endoscopy demonstrated minor esidual mucosal inflammation in eight patients.

omplications

There were no deaths. Postoperative complications arose in ive patients: wound infection in two, and anastomotic leakage, urinary tract infection and thrombophlebitis secondary to central venous catheterization in one each.

Discussion

This study revealed a pattern in which the extent of mucosal inflammation usually exceeded that of both serositis and fat-wrapping, whereas thickening of the bowel wall could be present without concomitant mucositis. This pattern was less evident in patients undergoing reoperation for Crohn's disease or in those with fistula or abscess, when serosal inflammation and fat-wrapping were commonly found in bowel without mucositis. These findings indicate that external changes of the bowel wall are unreliable guides to the extent of mucosal inflammation in Crohn's disease.

Thickening of the bowel wall was the feature found to be most extensive, often without concomitant mucosal or serosal inflammation, which may support the concept that Crohn's disease is caused by vasculitis and initiated in the bowel wall[5]. On the other hand, mural thickening may be unrelated to inflammation *per se* and may be a consequence of muscular hyperplasia secondary to stenosis. In patients without previous surgery or intra-abdominal infectious complications, serositis and fat-wrapping were accompanied by the most severe mucosal changes such as deep ulcers, cobblestoning and stricture, whereas small superficial ulcers were sometimes unaccompanied by external changes. These observations indicate sequential development of the inflammation in Crohn's disease, with superficial ulcers preceding deeper ulcers, fat-wrapping and serositis. They are in accord with findings of a previous endoscopic study of recurrent ileocolic inflammation, in which superficial ulcers were primary to deep ulcers and stricture[8]. It is probable that serositis and fat-wrapping are secondary to deep mucosal inflammation, but they may also be secondary to adhesions after previous surgery, or to abscess or fistula. Consequently, the appearance and extent of mucosal inflammation are relevant to the choice of surgical procedure and the extent of intestinal resection.

Supplementary endoscopic information on the extent of mucositis and stricture influenced surgical decisions in over 60 per cent of the present patients, usually saving bowel from resection. This accords with a previous report of a change in operative policy after intraoperative endoscopy in 47 per cent of cases[18]. In some of the present patients, however, endoscopic findings of normal mucosa could not guide the resection because of complex fistulas or heavily inflamed mesentery requiring larger *en bloc* resections.

Because Crohn's disease commonly requires reoperation, it is essential to minimize the extent of resection to reduce the risk of short bowel syndrome and diarrhoea. Preoperative radiology can both overestimate and underestimate the extent of intestinal inflammation, but intraoperative endoscopy may be used in selected cases to explore the small bowel if radiological findings are equivocal. In two of the present patients with previous resection and severe symptoms refractory to medication, intraoperative endoscopy revealed at most minor inflammation for which resection was unnecessary. As recently reported, decisions on resection are difficult if external indicators are absent[19]. In such cases enteroscopy may also prove valuable.

In extensive small bowel disease, endoscopy can identify strictures suitable for repair probably with a greater accuracy than measurement of stricture diameter with a balloon[4].

Intraoperative intestinal endoscopy is safe and simple, although in patients with a short or inflamed mesentery or with extensive adhesions it may be difficult to advance the endoscope. In this series, there was at worst minimal faecal contamination of the peritoneum. The complication rate was low, as in other reports of surgery for Crohn's disease[20,21]. It was found that bowel preparation with oral polyethylene glycol gave better cleansing of the small intestine than oral laxatives and facilitated endoscopic visualization. Interpretation of the endoscopic findings requires some experience, but the technique should be useful in many operations for Crohn's disease.

There is no consensus on strategy for resection in Crohn's disease. Many centres limit resection to all grossly inflamed intestine and wide radical resection has been abandoned. Intraoperative endoscopy provides new variables to be included in decisions, with precise information on the extent of mucositis and possible residual inflammation. This information is probably important for understanding the course after surgery and may be helpful in planning postoperative medication. Microscopic inflammation at the resection margin has no effect on the recurrence rate[22,23]. Whether minor residual inflammation is wholly without consequence for the future course remains to be studied. The precise estimation of the extent of mucositis that can be obtained with intraoperative endoscopy should be useful for further analysis of various surgical strategies.

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ranslocation of enteric bacteria 1 humans

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cterial translocation is the subject of considerable interest as possible cause of sepsis, particularly in critically ill patients. is defined as the passage of viable enteric bacteria across an tact mucosa to normally sterile tissues such as the regional mph nodes.

Translocation has been documented in animals under a riety of experimental conditions known to be associated with ucosal atrophy, such as prolonged starvation and the ministration of total parenteral nutrition[1]. A recent article[2] ggested that the same is true in humans, but little direct idence exists to confirm this suggestion. The aim of the present ıdy was to determine whether bacterial translocation could detected in a prospective study of surgical patients.

Patients and methods

Any patient in whom operation afforded access to the peritoneal cavity was studied, excluding those receiving preoperative antibiotics and those subsequently found to have generalized purulent or faecal peritonitis. Informed consent was obtained from all patients. Immediately after incision of the parietal peritoneum and before administration of any antibiotic prophylaxis, a mesenteric lymph node and serosal biopsy were taken from the terminal ileum using a clean surgical blade. The tissue was placed in sterile physiological saline and sent for routine bacteriological culture. A venous blood culture was also obtained. The operation was then undertaken.

Patients were monitored after operation to detect septic complications such as wound infection, chest infection and intraperitoneal sepsis.

Results

A total of 114 patients of mean age 63 (range 18–88) years were studied, comprising 58 men and 56 women. Of the procedures, 62 (54 per cent) were performed for malignant disease. In all, 58 operations (51 per cent) were elective colonic resections, the remainder being mainly cholecystectomy, appendicectomy, small bowel resection, gastrectomy, vagotomy and aortic grafting.

Bacterial translocation was established by a positive tissue culture in 18 patients (16 per cent); the organisms isolated are shown in *Table 1*.

Postoperative septic complications occurred in five (28 per cent) of the 18 patients with proven translocation and in 13 (14 per cent) of the 96 in whom translocation had not taken place.

ıble 1 *Bacterial species isolated from 18 patients with proven translocation*

atien).	Sex	Age (years)	Lymph node	Serosa	Venous blood
	M	40	*Klebsiella oxytoca*	*Klebsiella oxytoca*	—
	M	38	—	*Enterobacter cloacae*	—
	M	82	*Escherichia coli*	—	*Escherichia coli*
	F	79	—	*Proteus mirabilis*	—
	F	54	*Escherichia coli*	—	—
	F	70	*Escherichia coli*	—	—
	M	71	*Escherichia coli*	—	—
	M	31	—	*Escherichia coli*	—
	F	86	*Escherichia coli*	—	—
	F	66	*Escherichia coli* *Bacteroides fragilis*	—	—
	F	70	—	Diphtheroids	*Staphylococcus epidermidis*
	F	86	*Citrobacter freundii*	*Citrobacter freundii*	*Citrobacter freundii*
	F	81	*Escherichia coli*	*Escherichia coli*	—
	F	80	*Escherichia coli* *Bacteroides fragilis* *Streptococcus milleri*	*Escherichia coli* *Bacteroides fragilis* *Streptococcus milleri*	*Streptococcus acidominimus*
	F	24	*Escherichia coli* *Bacteroides fragilis*	—	—
	F	71	*Klebsiella aerogenes*	—	—
	F	77	*Escherichia coli* *Proteus morganii* *Clostridium sporogenes*	*Escherichia coli* *Morganella morganii* *Clostridium sporogenes*	—
	F	73	*Escherichia coli* Diphtheroids *Enterococcus durans*	*Escherichia coli* Diphtheroids *Enterococcus durans*	—

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Discussion

The translocation of enteric bacteria is proven in animal studies[1] but not well documented in humans. Two small studies based on the culture of mesenteric nodes have reported incidences of 4 per cent (one of 25)[3] and 17 per cent (seven of 41)[4]. The present paper describes a larger series and has found an overall incidence of 16 per cent. Blood culture produced the same organism as that isolated from the tissue in two patients; bacterial colonization of the tissue from blood is therefore a possibility, although the converse is also conceivable. In the remaining 16 patients blood culture was either negative or grew an organism different from that isolated from the lymph node and serosa, implying direct colonization from the gut.

The isolation of *Bacteroides* species in three patients is notable because anaerobic and Gram-positive bacteria have been found to translocate only rarely in animal studies[5]. Ambrose *et al.*[4] isolated *Bacteroides* from the mesenteric nodes of a number of patients with Crohn's disease but not from control patients without this condition. Why anaerobic bacteria rarely translocate and the mechanism by which translocation occurs remain unknown.

Bacterial translocation in the present study was associated with a twofold increase in the incidence of postoperative septic complications, but this difference was not statisti significant. The study continues and aims to identify subgr of patients at high risk of translocation. Any link bet translocation and villous atrophy will also be investigate

In conclusion, translocation of enteric bacteria does c in humans and may predispose to septic complicatior surgical patients.

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Announcement

Eurosurgery '93

The 3rd European Congress of Surgery under the auspices of Eurosurgery will take place in London from 14 to 17 September 1993. This international congress embraces all the specialties within surgery and sessions will be sponsored by all of the surgical specialist associations and societies of the participating nations, ensuring that there will be an international and multidisciplinary approach to many common surgical problems. Additionally, there will be European symposia of general interest to all surgeons on themes such as endoscopy, management of patients with trauma, daycase surgery, graduated patient care, surgical audit and surgery in the developing world. A major session on surgical training is also being organized by the surgical trainees' associations.

A large number of free papers will also be given and these communications will be published in a special supplement of *The British Journal of Surgery*.

On 14 September 1993 a number of satellite sessions sponsored by companies are being organized for delegates.

Further details and registration forms may be obtained from the Congress Secretariat, Eurosurgery 1993, Conference Associates and Services Ltd, Congress House, 55 New Cavendish Street, London W1M 8RE, UK. Telephone: 071 436 0531. Facsimile: 071 935 7559.

J. P. S. Lumley

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Extended left hepatectomy: technical aspects of an evolving procedure

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Lessons learned in an operative experience of 14 patients submitted to extended left hepatectomy for the management of liver tumours are presented. There were no deaths within 30 days of operation. Essential preoperative studies, indications and technical details of the operation are described. The importance of the morphology of the tumour and the influence of the tumour on the technique to be adopted are emphasized. Modifications of technique that allow selection of patients for the procedure, control of venous bleeding, accurate identification of the sectoral portal pedicles within the right liver and definition of the plane of parenchymal transection are addressed.

dvances in the understanding of liver anatomy have allowed e description of a range of surgical procedures for resection ased on control of the portal triads and the hepatic veins lated to the area of tissue to be excised. The description of ese procedures has varied but the anatomical classification sectors and segments of the liver described by Couinaud[1] is ow widely accepted and is the basis for the nomenclature pplied to the various operations[2]. Thus, for practical purposes, ere are five types of major resection[1] (*Table 1*). (The ternative terminology proposed by Goldsmith and Woodburn[3] also listed.)

There is now extensive surgical experience of major liver section, with the procedures of right and left hepatectomy nd right and left lobectomy being well described. By contrast, tended left hepatectomy, which achieves resection of segments , III, IV, V and VIII (and sometimes of segment I as well) *igure 1*), has not gained wide acceptance and is infrequently pplied. This has resulted from a failure to appreciate the otential resectability of some large lesions and to reports of gh morbidity and mortality rates accompanying the peration[4–9].

Couinaud[10] suggested the possibility of extended left epatectomy in 1954 but it was not until Starzl *et al.*[4] published e technique and results in four patients that the procedure as adequately described. Starzl *et al.* referred to the operation s left trisegmentectomy and accurately detailed the necessary ilar dissection. Difficulty in defining a plane of parenchymal ansection on the right side and of controlling haemorrhage

able 1 *Anatomical classification of major hepatic resections*

ouinaud[1]	Goldsmith and Woodburn[3]
ight hepatectomy (segments V, VI, VII and VIII)	Right hepatic lobectomy
eft hepatectomy (segments II, III and IV)	Left hepatic lobectomy
ight lobectomy (segments IV, V, VI, VII and VIII; sometimes also segment I)	Extended right hepatic lobectomy
eft lobectomy (segments II and III)	Left lateral segmentectomy
xtended left hepatectomy (segments II, III, IV, V and VIII; sometimes also segment I)	Extended left lobectomy

ight lobectomy (extended right hepatic lobectomy) has also been eferred to as right trisegmentectomy and this term is commonly found the literature. Similarly, extended left hepatectomy is referred to as ft hepatic trisegmentectomy[4]

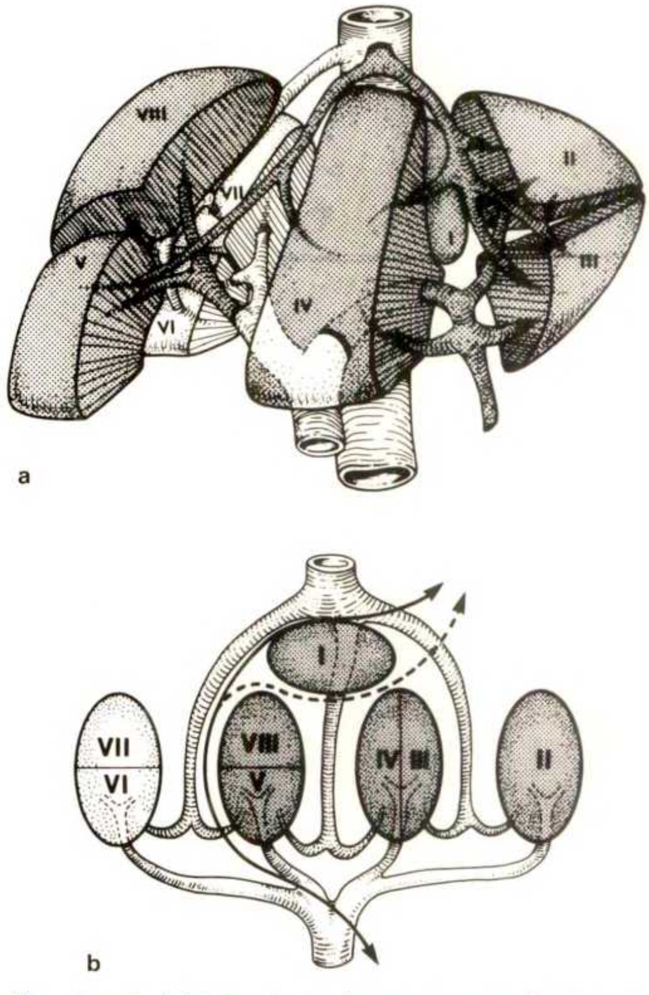

Figure 1 **a** *Exploded view showing the sectors, separated by the major hepatic veins, and the segmental structure of the liver. Each segment is supplied by a portal triad. The segments removed in extended left hepatectomy (I, II, III, IV, V and VIII) are stippled. (Segment I is not always resected.) Dark bands on the left portal triad and right anterior sector branch of the right triad mark the points of division during operation. Note that the procedure leaves the posterior right hepatic sector (segments VI and VII) and right hepatic vein together with the right posterior sector triad intact. The middle and left hepatic veins are divided flush with the inferior vena cava at the point marked by the dark band.* **b** *Schematic representation of the segments shown in* **a**. *The lines of transection if the caudate lobe is removed (—) or retained (– – –) are shown*

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and biliary complications was recognized. Indeed, blood loss in the four patients ranged from 2·7 to 20 litres and two developed biliary fistula and/or stricture[4]. That report highlighted the main technical problems and attendant risks and stimulated others to attempt the operation. Reports of small numbers of patients have continued to appear but problems remain; biliary complications were reported by Hasegawa *et al.*[5] and Al-Hadeedi and colleagues[6] in two of six and three of five patients respectively.

This report describes a standardized technique for extended left hepatectomy and outlines preoperative evaluation. The use of a morphological classification of hepatic tumours in defining resectability is emphasized[11].

Patients and methods

Preoperative evaluation

Anatomical assessment is of paramount importance and radiological imaging should not exclude patients from operation on the basis of size of the tumour alone. Even patients with very large tumours that expand and compress the surrounding tissue and displace blood vessels and bile ducts ('pushing' tumours) should be selected for laparotomy[11]. Computed tomography (CT) is important in suggesting the expansile form of tumour (*Figure 2*), and displacement of hepatic and portal vessels can be confirmed by hepatic arteriography and late-phase portography. Ultrasonography, including Doppler imaging of the portal and hepatic veins, is also valuable in this regard. Evidence of displacement of vessels, even when closely adjacent to tumour, suggests resectability[2]. Inferior venocavography and hepatic venography are performed in patients in whom very large tumours situated posteriorly are considered to compromise the right hepatic vein or inferior vena cava.

Although endoscopic retrograde cholangiography (ERC) is not necessary for other forms of major hepatic resection, the authors have used it in patients about to undergo extended left hepatectomy since it may help to define the anatomy of the anterior and posterior sector hepatic ducts on the right and any associated biliary anomalies at the liver hilum. The frequent occurrence of a right posterior sector hepatic duct draining into the main left hepatic duct system[12], although creating an anatomically difficult situation at operation, does not necessarily indicate irresectability.

A diligent search is always made for extrahepatic disease using CT of the thorax and radionuclide scintigraphy of the bones. Evidence of hepatic insufficiency in the form of abnormal liver function test results, an abnormal clotting profile, demonstrable cirrhosis or ascites is also a contraindication to resection. Vascular and biliary anomalies are important; the rare absence of the right portal vein[13] makes th operation impossible.

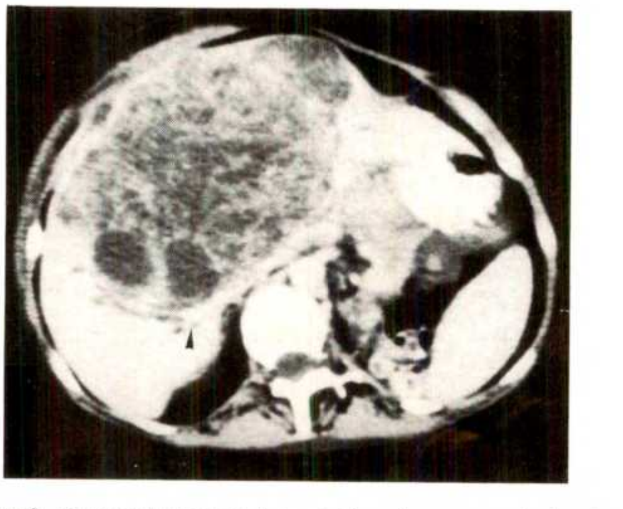


Figure 2 *Computed tomogram demonstrating a large metastatic deposit from a primary renal carcinoma. The tumour occupies the left liver including the greater part of segments II, III, IV, V and VIII, and extends into segment I. The posterior sector pedicle is displaced by the tumour, which is pushing posteriorly (arrow). The posterior sector of the liver is free from tumour. Displacement of the posterior sector pedicle was confirmed by hepatic arteriography and late-phase portography. Extended left hepatectomy was carried out and the patient remains alive and well $5\frac{1}{2}$ years after operation*

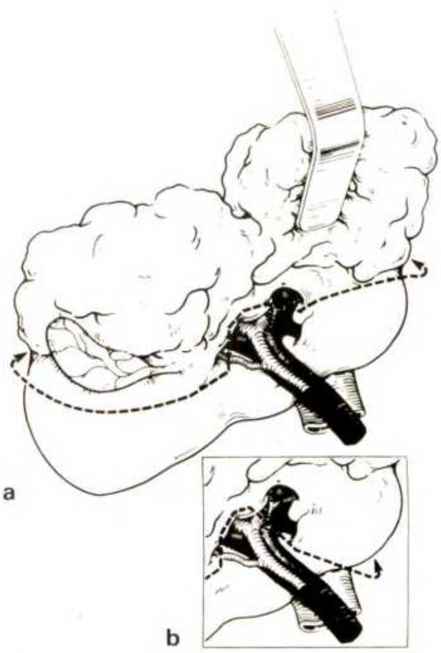


Figure 3 *The left lobe of the liver has been mobilized and turne upwards and towards the right. The initial approach during extended le hepatectomy allowing dissection of the portal triad and other structur is illustrated from the left posterolateral aspect. The line of futur transection (---) is indicated* **a** *with and* **b** *without retention of th caudate lobe. When this lobe is preserved, the left portal vein is ligate and divided beyond its caudate branch. If the caudate lobe is to b removed, then the portal vein can be ligated more proximally. The lin of transection runs along the obliterated ligamentum venosum and the across the base of the quadrate lobe and hilum before curving to th right, extending into the right fissure lateral to the gallbladder fossa an just anterior to the right hepatic vein*

Surgical technique

A bilateral subcostal incision is used with a short midline extension It may be necessary to remove the xiphisternum to allow maximun access. It is not usually necessary to extend the incision into the ches and this is avoided when possible.

After division of the falciform ligament backwards to the vena cava intraoperative ultrasonography is performed to confirm the anatomica configuration of the tumour and major hepatic veins. In particular, a attempt is made to identify a large inferior right hepatic vein. Presenc of such a vein augments drainage of segment VII and may even allov the right main hepatic vein to be sacrificed during operation[14].

An important aspect of assessment of the tumour (and indeed o the operative technique) is full mobilization of the liver, not only b division of the left triangular ligament, but also by complete divisio and mobilization of the ligament on the right. This not only allow palpation of segment VII for the presence of additional tumour but i essential later in the procedure for the identification of the correct plan of parenchymal dissection (see below). Regional lymph nodes that ar enlarged are removed to define the presence of nodal metastases.

Initial dissection is identical with that for left hepatectomy. The lef liver is turned to the right side and the portal triad approached fron the left. The point of ligation of the vessels to the left liver is dictated by involvement of the caudate lobe (segment I) by tumour. If segmen I requires resection, the left hepatic artery, bile duct and portal vei must be ligated close to the hilum so as to interrupt the blood suppl to segment I as well as that to the left liver. However, as described b Starzl *et al.*[4], when segment I is to be preserved the structures of the left portal triad are secured in the base of the umbilical fissure so as to leave the blood supply to segment I intact (*Figure 3*).

After vascular control at the hilum has been obtained, the left hepatic vein and the left of the subdiaphragmatic inferior vena cava are completely dissected. It is usually possible to control the left hepatic vein preliminarily. Such control, and indeed that of the middle hepatic vein, is anatomically feasible as both veins have an extrahepatic portion in 95 per cent of instances[15]. If, however, it should prove difficult to te these veins, and in particular the middle hepatic vein, they can xposed at a later stage during parenchymal transection (see below).

There has been some difficulty in the past in defining the line of sion of the liver capsule which lies well to the right of the principal sura, which by this stage of the procedure is already well demarcated.

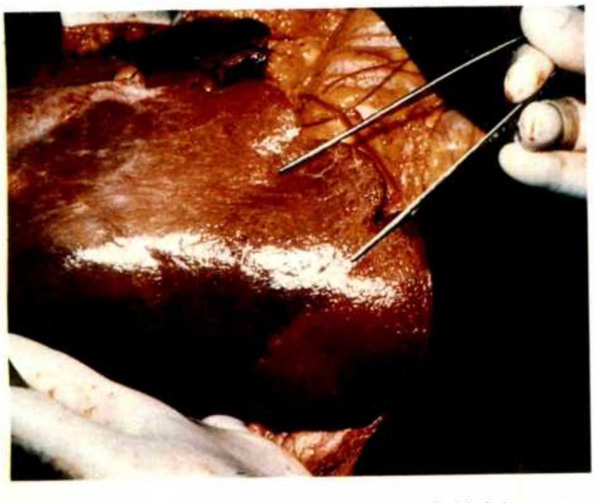
plane of transection is horizontal, lateral to the gallbladder fossa parallel and just anterior to the right scissura. It is important to ne the plane of parenchymal transection, which should not only s anterior to the right hepatic venous trunk but allow division of anterior sector branch of the right portal triad while preserving avoiding damage to the posterior sector triad (*Figure 1*). Although e are no reliable surface markings, a plane extending from the rior border of the right hepatic vein above and extending izontally so as to emerge well to the right of the gallbladder fossa gnates the correct position within the parenchyma. This line can accurately defined when it is possible to clamp the portal pedicle he anterior right sector of the liver. This is possible within the enchyma[16] close to the hilum in cases in which the tumour does extend so near to the right main pedicle as to make access impossible hout compromising tumour clearance. If the right anterior sector icle is clamped and the right posterior sector pedicle left intact, a of demarcation extending along the right scissura rapidly develops *gure 4*).

The parenchymal phase is carried out from below upwards and is ed by an intermittent Pringle manoeuvre applied for periods of up 15 min. Although the Pringle manoeuvre can be carried out for ger[17,18], this has not been the present authors' practice.

If significant bleeding occurs during the parenchymal phase of nsection of the liver, it usually arises from the hepatic veins or vena a; this is particularly true in extended left hepatectomy as the plane lissection lies in the right scissura just anterior to the right hepatic n. It has been the authors' practice to place the patient in a 15° d-down position and to ensure that the central venous pressure nains low (approximately 5 cmH$_2$O) during the whole of this period. s reduces blood loss from the hepatic veins and minimizes the risk significant air embolism, which has not occurred in a large number major hepatic resections during which this technique has been used. addition, continued bleeding from transected branches of the right atic vein can be visualized and controlled.

Parenchymal transection is performed by the tissue-fracture hnique using a Kelley clamp but may be less traumatic by the use a suitable parenchymal dissector[19]. Once the right anterior sector licle has been identified, dissection is kept anterior to the right sterior sector pedicle. The structures of the portal pedicles are dense d white as opposed to the hepatic veins and are readily visualized.

It is important to note that in many very large tumours the growing ion produces a narrow zone of compressed atrophic liver tissue. hough tumour clearance is narrow, it can be achieved by peeling lesion away from the residual parenchyma in this atrophic plane.



gure 4 *Operative photograph illustrating extended left hepatectomy. he vessels to the left liver have been controlled and the right anterior ctor vessels have also been clamped. The forceps illustrates the marcation line that was defined between the right and left liver (upper ade of the forceps) and between the right anterior sector (between the ades of the forceps) and right posterior sector (behind the line of marcation and still vascularized). The line of incision is along the fined plane*

Proceeding with the dissection upwards and medially, the parenchyma is divided. With large tumours, the plane of dissection is dictated by the lesion. As the middle hepatic vein is encountered, it is controlled within the line of transection and the liver parenchymal division is completed.

After removal of the resected specimen, the remnant (segments VI and VII) presents an *en face* raw surface area. If central venous pressure has been kept low, bleeding is easily identified and controlled. Intermittent use of the Pringle manoeuvre allows similar control of bleeding from branches of the hepatic artery or portal vein. Any visible open bile ducts are closed with fine resorbable sutures (4/0 Vicryl; Ethicon, Somerville, New Jersey, USA). The raw surface may be coated with fibrin glue (Tissucol; Immuno, Zurich, Switzerland) and an argon beam coagulator can be used for final haemostasis. The omentum is then laid over the divided surface. Two tube drains are inserted.

Results

The senior author currently has experience of extended left hepatectomy performed to remove tumour in 14 patients. All had primary or metastatic carcinoma. There have been no operative deaths. The initial seven patients were operated on in London, UK, and were included in an earlier report[20]. In this initial series, one patient suffered a prolonged biliary fistula and subsequently developed biliary stricture at the junction of the right anterior and posterior sector ducts. This stricture responded to endoscopic balloon dilatation. Of seven patients operated on in Berne, blood loss during the procedure ranged from 0·5 to 2·3 (mean 1·4) litres. One patient developed a temporary biliary fistula that closed spontaneously within 7 days. Two patients developed subphrenic fluid collections that were drained uneventfully under ultrasonographic control. All patients recovered with good liver function and were discharged from hospital. Full details of this series will be published when sufficient follow-up is available.

Discussion

This paper describes the important preoperative and intraoperative manoeuvres necessary for the safe performance of extended left hepatectomy. The description by Starzl *et al.*[4] of the essentials of the procedure is important, but subsequent experience with this radical operation has yielded some significant technical points especially concerning assessment of resectability, precise definition of the plane of parenchymal liver transection and prevention of excess blood loss and biliary damage.

Preoperative evaluation

Preoperative assessment has two principal objectives. First, it is important to establish the appropriateness of the procedure and the functional capacity of the residual liver mass. Attempts to assess hepatic functional reserve using clearance techniques have proven unreliable. It is the authors' experience that it is sufficient, in this and other extensive liver resections, to have normal or near-normal liver function test results together with radiological evidence of an adequate blood supply and hepatic venous drainage and the absence of cirrhosis. Second, it is important to assess the anatomical boundaries of the tumour and to combine this with a diligent search for extrahepatic disease.

It is inherent to the indications for extended left hepatectomy that operation be performed for large solitary tumours extending from left to right or for left-sided tumours with satellite lesions extending into the right anterior sector of the liver. Radiological investigations are directed so as to display the gross morphological anatomy of the tumour and related vessels and biliary structures. In a previous report, liver tumours were classified into pushing, hanging and invading types[11]. This simple classification has particular value in assessment for extended left hepatectomy. The pushing variety of tumour, even when the lesion is seen to be extremely large on initial CT, tends not to invade surrounding structures but to displace the portal pedicles and hepatic veins. This expansion compresses a fine layer of atrophic liver tissue in advance of the tumour that lies between the lesion and the vascular structures. This zone is of importance during later parenchymal dissection. Appreciation of the pushing nature of the lesion means that even very large and apparently irresectable tumours may be resectable[21]. Although it has been argued that angiography before hepatic resection is not essential (and indeed this is the case with peripherally sited lesions well away from the hilar structures and vena cava), we strongly advocate angiography before extended left hepatectomy for large tumours, which frequently encroach on the portal triad at the hilum of the liver and lie adjacent to or compress the inferior vena cava. Doppler ultrasonography may also be of value in demonstrating the patency of major vessels before operation. ERC has recently been used before extended left hepatectomy because it has the advantage of demonstrating variations in the confluence of the anterior and posterior right sector hepatic ducts. As such variations are frequent[12] and influence preoperative and intraoperative decisions, their demonstration seems valuable.

In general, preoperative studies dictate two approaches to the procedure. Where the tumour is very large and is compressing and displacing the vessels to the posterior sector of the right liver, the line of parenchymal transection will be dictated by the tumour itself and is essentially performed within the peripheral fibrous zone surrounding the lesion. On the other hand, a less extensive tumour of the invasive or pushing variety that does not impinge on the structures to the right posterior sector allows a transection within normal parenchyma and permits greater tumour clearance.

Surgical technique

The two major problems in the hepatic parenchymal transection phase are the significant blood loss that may occur during the operation and possible damage to biliary structures resulting in postoperative biliary fistula and/or stricture. The technique described previously[2], in which dissection starts from below and proceeds upwards, helps to reduce these problems. Difficulties in defining the plane of transection can be resolved by the method of selective clamping (or division) of the portal triad (pedicle) to the anterior right sector before starting the parenchymal phase[16] or by the use of intraoperative ultrasonography. This approach, together with the maintenance of a low central venous pressure and a consequent decrease in hepatic venous pressure during parenchymal transection, has proven valuable in contributing to reduced blood loss. In no patient have the present authors used hepatic devascularization or isolation[17,18] for major liver resection.

Avoidance of biliary complications centres on the approach to the control of the right anterior sector hepatic pedicle with preservation of the posterior sector vessels and hepatic duct. Control close to the hilum usually solves this problem but is difficult in patients in whom the bifurcation of the pedicle is intrahepatic or when its position is distorted by tumour. Control can usually be readily achieved if the dissection is carried out with caution so that direct vision is not hampered. Tubal splintage has been recommended to help identification of the relevant right hepatic ducts[4] but this has not been the present authors' practice. Using the approach described, together with information provided by preoperative ERC, the authors' most recent seven patients have been operated on with only one temporary postoperative biliary fistula. Two bile leaks occurred but did not cause morbidity and both responded to percutaneous drainage.

Successful extended left hepatectomy depends on good and well interpreted preoperative investigation, precise identification of the plane of parenchymal transection, control of central venous pressure, and avoidance of biliary complications. The operation can be carried out with an acceptable mortality rate and reasonable level of morbidity.

Acknowledgements

Figure 1 was drawn by Susan Neil, Medical Illustrator; *Figure 3* reproduced with permission of the publisher, Churchill Livingstone

Addendum

Since submission of this paper, a further eight patients have undergo extended left hepatectomy at Memorial Sloan–Kettering Canc Center, New York. There were no deaths and two temporary bilia leaks.

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aparoscopic treatment of a ver hydatid cyst

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veral procedures have been described for the treatment of patic hydatid cyst, ranging from simple puncture to liver section and transplantation, although the most commonly ed technique is total or partial cystopericystectomy[1,2]. This per reports a hydatid cyst treated with laparoscopic surgery nsisting of partial cystopericystectomy, intraoperative olangiography and cholecystectomy.

ırgical technique

65-year-old woman was admitted with a 1-year history of pain in e epigastrium and right hypochondrium, radiating to the back. She d neither fever nor jaundice. Laboratory tests revealed slight sinophilia with normal leucocyte count. Abdominal ultrasonography d computed tomography showed a 6 × 8 cm unilobar cyst, with nse contents, located in segment IV of the liver. The lesion was closely lated to the gallbladder and of appearance compatible with a hydatid st (*Figure 1*). Hydatid disease was confirmed by indirect haemag-utination and immunoelectrophoresis. The woman underwent paroscopic partial cystopericystectomy and drainage of the residual st cavity, with cholecystectomy and transcystic intraoperative olangiography.

The patient was positioned with legs apart and the surgeon standing tween them. The assistant stood at the left of the patient and the deomonitor was set on the right. Pneumoperitoneum was created by nbilical puncture using a Veress needle and intra-abdominal pressure as controlled automatically at 15 mmHg. A straight 0° telescope tached to the videomonitor was inserted through a 10-mm umbilical nnula and examination of the abdominal cavity was performed. The ver hydatid cyst was visualized in segment IV, close to the gallbladder. nother three cannulas were inserted: one of 5 mm to the right of the mbilicus, another of 10 mm to the left of the umbilicus and a third f 5 mm to the left of the xiphoid process (*Figure 2*). A 6-Fr catheter as inserted through the abdominal wall into the cyst capsule.

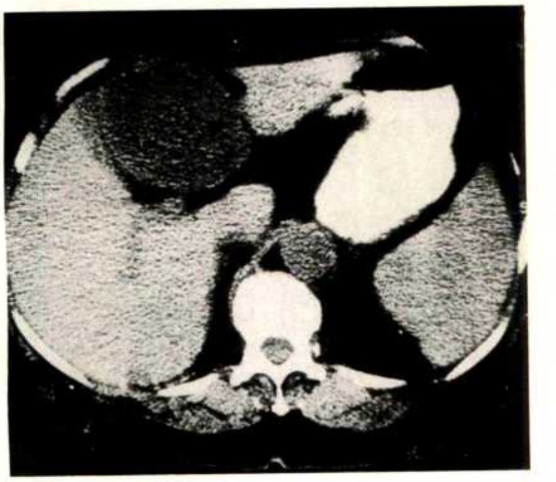

Figure 1 *Computed tomogram showing the cyst within segment IV of he liver*

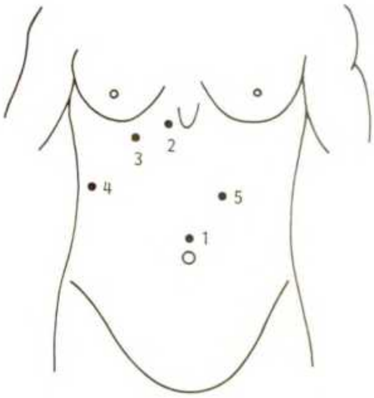

Figure 2 *Positions of cannulas. 1, 10-mm cannula for the straight telescope and videocamera; 2, 5-mm cannula for the irrigation–suction and palpation probe; 3, 10-mm cannula for lavage of the cyst; 4, 5-mm cannula for the atraumatic grasping forceps; 5, 10-mm cannula for instruments (scissors, clip applicator)*

Hypertonic saline was injected and left for 10 min. A 10-mm cannula was inserted into the cyst capsule through the site of the abdominal puncture and a thick yellow fluid containing vesicles and membranes was aspirated, using irrigation and suction at intervals until a clear clean fluid was obtained. At no time was there spillage of fluid into the abdominal cavity. The cannula was withdrawn and the straight telescope was inserted into the cyst; this showed an absence of vesicles and a clean cyst cavity.

Even though the patient had not presented with cholestasis or cholangitis, there remained the possibility of a communication with the bile duct. A transcystic intraoperative cholangiogram was obtained. The bile duct measured 7 mm and contained no parasites, with free passage of contrast to the duodenum and no communication with the cyst cavity. Cholecystectomy was performed, with resection of the projecting part of the cyst, which was free from adhesions and clear of the liver parenchyma. A Penrose-type drainage tube was left inside the cyst cavity. The gallbladder and capsule were extracted through the umbilical cannula. The operation lasted 90 min.

The postoperative course was uneventful and a liquid diet was started on day 1 after surgery, with the patient allowed to get up the same day. The drain was removed on day 5 and the patient discharged from hospital on day 6. Histological examination of the cyst capsule confirmed hydatid disease.

Discussion

Partial cystopericystectomy with removal of all the projecting capsule of the liver parenchyma is an efficient surgical treatment for liver hydatid disease[3]. Peripheral and unilobar hydatid cyst, whether complicated or not, can be treated with laparoscopic surgery using partial cystopericystectomy and drainage as described above. The cyst fluid should be sterilized with hypertonic saline, which is an effective scolicidal agent and appears to be safe even when a biliary communication exists[4]. This technique prevents the cyst contents from leaking into the abdominal cavity, thus avoiding contamination. To detect any communication of the cyst with the bile duct, intraoperative transcystic cholangiography was performed. Daughter vesicles in the bile duct may be suspected before operation from clinical evidence of cholestasis or cholangitis, or from ultrasonography or cholangiography. Such vesicles must be extracted, by preoperative endoscopic sphincterotomy, or choledochotomy at laparotomy or laparoscopy, depending on the surgeon's experience.

In conclusion, a liver hydatid cyst has been treated by laparoscopic surgery with its advantages of less postoperative pain, little or no ileus, short hospital stay, quick return to work and more aesthetic result[5,6].

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Case report

Br. J. Surg. 1993, Vol. 80, July, 908

Biliary stent failure after 42 years

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This case illustrates the use of a vitallium tube to repair iatrogenic injury to the common bile duct. These tubes were first used in the USA in the 1940s. The 42-year symptom-free period described is remarkable.

Case report

A 48-year-old woman underwent cholecystectomy for cholelithiasis in June 1945. She had a problematic postoperative course and was told that damage to the bile duct had occurred. A second operation relieved symptoms. The woman remained well until 1987, when she presented with a 5-day history of diarrhoea, vomiting and weakness.

On examination the patient was apyrexial and tachypnoeic with a sinus tachycardia but no jaundice. Investigations demonstrated leucocytosis of 31·3 × 10^9/l, a haemoglobin concentration of 13·3 g/ and an erythrocyte sedimentation rate of 85 mm/h. Liver function tes revealed a serum bilirubin level of 30 μmol/l with an alkalin phosphatase activity of 1205 units/l. Blood cultures grew *Klebsiel oxytoca*. A plain abdominal radiograph revealed a metal tube, 25 mm long, in the right upper quadrant. Ultrasonography did n demonstrate biliary obstruction. *Klebsiella* septicaemia secondary t ascending cholangitis due to the biliary stent was diagnosed. Aft intensive antibiotic therapy, endoscopic retrograde cholangiopancreatography was performed at which a shiny metallic object was identifie protruding into the postbulbar region of the duodenum. It is not clea whether the tube had been used to stent a choledochoduodenostom or had eroded into the duodenum to form a biliary–enteric fistul Retrograde injection of contrast medium revealed debris proximal t the metal tube (*Figure 1*). The blocked tube (*Figure 1*, inset) wa removed endoscopically with a Dormia basket.

The patient's condition improved, liver function returned to norma and she remains well 5 years later with no symptoms attributable t the liver or biliary tract.

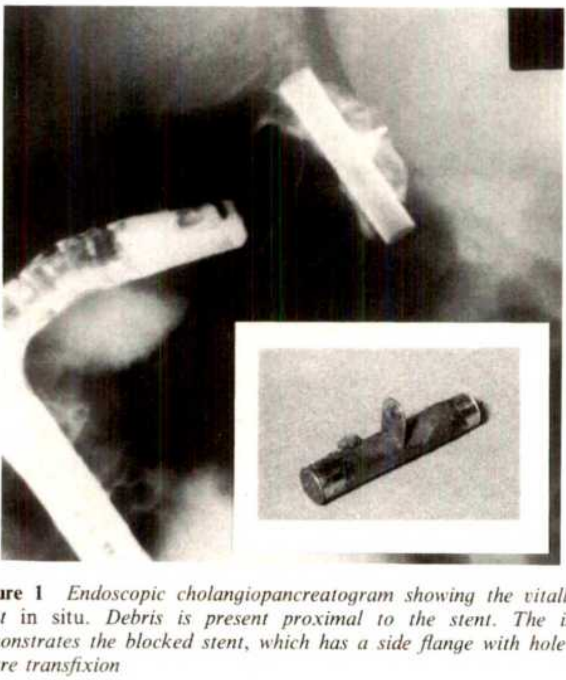

Figure 1 *Endoscopic cholangiopancreatogram showing the vitallium stent* in situ. *Debris is present proximal to the stent. The inset demonstrates the blocked stent, which has a side flange with hole for suture transfixion*

Discussion

This woman illustrates the remarkably long symptom-fre survival of a patient in whom a vitallium tube was inserted t treat a common duct injury. Vitallium tubes were described i the North American literature of the 1940s for the repair of th common bile duct[1] and for the treatment of benign stricture[2] Although there are no references in the UK literature thi patient demonstrates the use of these tubes in 1945 in th Manchester hospitals. This type of tube was first described b Pearce[2] in 1941, who reported patency 1 year after operation Migliaccio[3] reported an injury to the common hepatic duc after cholecystectomy that required repair over a Y shape vitallium tube. The patient was symptom-free 24 months afte surgery.

Vitallium tubes were thought to be virtually inert[4] althoug plugging with debris leading to recurrent jaundice was describe 6 months after insertion[5]. Follow-up data are lacking and the absence of references after 1945 suggests that they were n longer used.

A 42-year patency for a biliary stent is notable and the shiny condition of the metal tube on removal is a striking tribute t the resilience of vitallium in a constant stream of bile.

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Orthotopic liver transplantation for hepatic complications of Wilson's disease

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Thirteen orthotopic liver transplantations were performed in 12 patients for hepatic complications of Wilson's disease between May 1988 and July 1992. Ten patients had fulminant hepatic failure and two chronic liver disease. One patient underwent retransplantation for liver abscess secondary to hepatic artery thrombosis. Nine patients survive at a median follow-up of 18 (range 6–31) months. Three patients have died: two from multiple organ failure and sepsis; one from B cell lymphoma. Postoperative complications included bleeding requiring laparotomy in two patients, renal impairment in five, bacterial septicaemia in three, fungal sepsis in two and acute cellular rejection in six. The nine surviving patients are well with normal liver function test results.

Wilson's disease is an inborn error of metabolism characterized y defective biliary excretion of copper resulting in excessive ccumulation in organs such as the liver and brain, which ubsequently show degenerative changes. The most common resentation of the disease in adults is with neurological ymptoms that include progressive intellectual deterioration, remor, dysarthria and dystonia. Other less common features nclude haemolytic anaemia, haematuria, amenorrhoea and nusculoskeletal symptoms. In children and young adults, Wilson's disease commonly presents with liver disease that may ake the form of decompensated cirrhosis or fulminant hepatic ailure (FHF). Orthotopic liver transplantation (OLT) is now accepted as the only effective treatment of Wilson's disease presenting with FHF[1] and for chronic liver disease that has not responded to medical therapy. To date, the experience of nost centres is limited to a small number of patients or to individual case reports. This paper presents 12 patients who underwent OLT for hepatic complications of Wilson's disease over a period of 4 years.

atients and methods

Thirteen OLTs were performed in 12 patients (four male, eight female) or hepatic complications of Wilson's disease between May 1988 and uly 1992. The median age at presentation was 19 (range 8–33) years. Ten patients presented with FHF as defined by Trey and Davidson[2] and two with chronic liver disease. Eight patients with FHF were encephalopathic at the time of admission to hospital and two became o soon thereafter. Clinical features at presentation included a 'flu-like illness in five patients, malaise in seven and upper abdominal pain in five. Ten patients were jaundiced at presentation, three had hepatomegaly and nine splenomegaly. One patient with chronic liver disease presented with variceal bleeding. Kayser–Fleischer rings were present in eight cases. One patient presenting with chronic liver disease had neurological and psychological manifestations and complained of remors, difficulty in writing and depressive illness. No other patient n this series had neurological manifestations of Wilson's disease.

All ten patients with FHF had hyperbilirubinaemia (median 257 (range 54–885) μmol/l); their median serum aspartate transaminase level was 140 (range 32–400) units/l. These patients also had significant coagulopathy with a median prothrombin ratio of 3·0 (range 1·7–14·0). Four patients had renal impairment with a median serum creatinine evel of 235 (range 141–490) μmol/l. Six patients were noted to have anaemia associated with a raised reticulocyte count. Preoperative diagnosis of Wilson's disease was made in nine of the ten patients with FHF; Kayser–Fleischer rings were present in seven of these patients.

The diagnosis of Wilson's disease was made in the other two patients on the basis of raised levels of urinary copper and a low serum caeruloplasmin concentration. Serum copper studies showed a median value of 20·3 (range 12·0–41·2) μmol/l (normal 11–20 μmol/l) and the median serum caeruloplasmin level was 0·16 (range 0·07–0·54) g/l (normal 0·2–0·6 g/l). The median urinary copper excretion was 8·2 (range 0·7–21·1) μmol per 24 h (normal < 1·2 μmol per 24 h) (*Figure 1*). One patient with low urinary copper excretion of 0·7 μmol per 24 h had a value of 43·2 μmol per 24 h after penicillamine challenge[3].

The two patients who presented with chronic liver disease had both been treated with penicillamine. One female patient had received the drug for 12 years but 18 months before presentation had discontinued treatment and developed decompensated liver disease. The second patient was diagnosed 4 years before transplantation and had been receiving penicillamine; this was later changed to triene (tetraethylene tetramine dihydrochloride) because of severe thrombocytopenia. She underwent transplantation for deteriorating liver function and recurrent haematemesis from oesophageal varices secondary to portal hypertension.

All patients who presented with FHF were considered for OLT, as medical therapy is almost always ineffective for this group[1]. Six of the present ten patients received penicillamine for a period ranging from 4 to 14 days before operation, with no apparent clinical or biochemical improvement in condition. Preoperative management in these patients included the correction of coagulation disorders with plasmaphaeresis, fresh frozen plasma and cryoprecipitate. Four patients were electively ventilated before operation as they were in grade III or IV encephalopathy. Intracranial pressure was monitored using a Camino bulb[4] (Camino Laboratories, San Diego, California, USA) and intravenous mannitol used to reduce raised pressure[5].

At operation all but one of the patients had a cirrhotic liver associated with portal hypertension. The youngest patient who

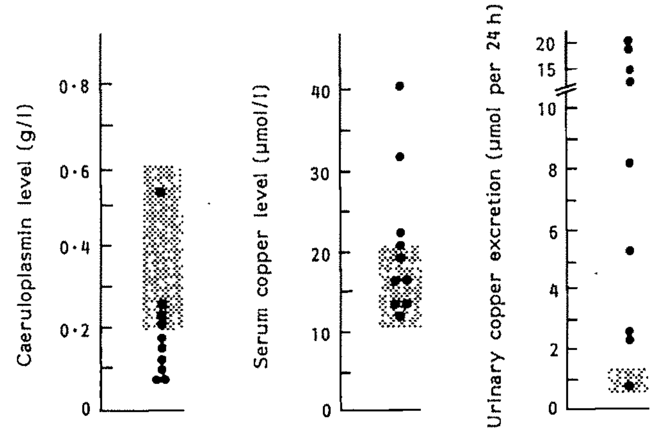

Figure 1 *Copper studies in ten patients with fulminant Wilson's disease.* ▨, *Normal range. One patient did not complete 24-h collection of urine for urinary copper estimation*

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presented with FHF had a shrunken non-cirrhotic liver with areas of nodular regeneration similar to those seen in acute viral hepatitis. Standard techniques for OLT were used[6]. The median blood loss at operation was 6·8 (range 1·7–18) litres. Venovenous bypass of the systemic and portal venous systems was used in eight patients; it was not performed in the four youngest. Postoperative immunosuppression was maintained in ten patients by standard triple immunotherapy using cyclosporin A, prednisolone and azathioprine; two patients received FK506 with low-dose prednisolone as part of a multicentre clinical trial.

Results

Thirteen OLTs were performed in 12 patients; one patient underwent retransplantation for pyogenic liver abscess secondary to hepatic artery thrombosis. Nine patients survive at a median follow-up of 18 (range 6–31) months. Three patients have died: two from multiple organ failure and sepsis in the early postoperative period, one from B cell lymphoma 7 months after transplantation. Two patients underwent a second laparotomy for postoperative bleeding, and one with pyogenic liver abscess had drainage and debridement of necrotic liver tissue.

Other postoperative complications included significant renal impairment requiring haemodialysis in five patients, adult respiratory distress syndrome in three, bacterial septicaemia in three, fungal sepsis in two, cytomegaloviral hepatitis in one and wound infection in three. Six patients had episodes of acute cellular rejection, confirmed by liver biopsy in the postoperative period, that responded to high-dose steroids. One patient developed a bile duct stricture secondary to hepatic artery stenosis; these were successfully treated by bile duct dilatation and hepatic artery balloon angioplasty. One patient developed nodular regenerative hyperplasia secondary to azathioprine toxicity. She presented with haematemesis secondary to oesophageal varices 2 years after transplantation and was found to have significant portal hypertension. This patient has since had a mesocaval shunt and is now asymptomatic. The nine surviving patients are well with normal liver function test results.

Pathological findings

Nine of the ten hepatectomy specimens from patients with a fulminant presentation were cirrhotic. The one exception was the liver removed from the youngest patient, which was shrunken and weighed 310 g. The cut surface showed broad areas of multiacinar collapse and discrete zones of nodular regeneration at the periphery. The histological appearance in this case was indistinguishable from that observed in viral hepatitis with a fulminant or subacute course, except for the presence of cytoplasm of surviving hepatocytes.

The nine cirrhotic livers were predominantly micronodular or had mixed nodules varying from 0·3 to 1·0 cm in size. The livers were of normal or slightly increased size (mean weight 1510 (range 1270–1860) g). There was significant piecemeal necrosis in seven organs. Hepatocanalicular cholestasis was severe in all cases, with periportal cholangiolar bile casts in five. Overall, chronic portoseptal inflammation was moderate. All livers showed areas of recent parenchymal collapse and/or coagulative necrosis and scattered spotty necrosis with or without clusters of neutrophils. Orcein staining revealed coarse copper-associated granules in a patchy distribution within hepatocytes, Kupffer cells and portoseptal macrophages. These granules stained with the rhodamine technique for copper, although the staining reaction was much weaker than with orcein in every case.

The remaining two patients with long-standing liver disease had macronodular cirrhosis (liver weight 1145 and 1200 g) and one liver showed adenomatoid regenerative nodules up to 2·0 cm in diameter. Histological analysis revealed no characteristic features and in only one case showed discrete orcein-positive deposits and cholestasis with evidence of an ischaemic type of coagulative necrosis.

Discussion

Hepatic manifestations lead to clinical presentation i approximately 40 per cent of patients with Wilson's diseas The majority present with chronic liver disease; presentatio with FHF is rare and occurs typically in children and youn adults[7]. Wilson's disease should always be excluded in childre and young adults who present with FHF. The diagnosis ma however, be difficult to establish: liver biopsy is often preclude because of the presence of severe coagulopathy and results o copper studies may be difficult to interpret. Although the serum caeruloplasmin level is often low, this may also occur in othe forms of FHF and is of no diagnostic value[8]. Estimations o urinary copper are not useful in the presence of renal failure.

The Kayser–Fleischer rings considered to be pathognomoni of Wilson's disease may be absent, particularly in youn patients presenting with hepatic complications[7]. Even thoug Kayser–Fleischer rings are said to be associated wit neurological manifestations, in the present series eight of 1 patients had such rings on slit-lamp examination but only on of these had neurological symptoms. The diagnosis of Wilson' disease in FHF is usually suggested by the relatively mild ris in levels of serum transaminases compared with the degree o acute hepatic insufficiency[8], by high serum bilirubin level, hig serum copper concentration and the presence of a non-immun haemolytic anaemia[8]. The presence of haemolytic anaemia i suggested by a raised reticulocyte count and a fallin haemoglobin concentration. These features in children an young adults with FHF should always raise the suspicion o Wilson's disease.

Surgery in patients with fulminant Wilson's disease is ofte demanding because of the combination of the underlyin cirrhosis and the presence of portal hypertension an coagulopathy associated with the fulminant presentation However, the median blood loss at operation in patients wit Wilson's disease in this series was not significantly differen from that in others with FHF or chronic liver disease.

Pathological findings in this series confirm a previou observation of liver cirrhosis in patients with Wilson's diseas and a fulminant presentation[9]. The only exception in the presen series was an 8-year-old Indian girl with an extremely collapsed liver that showed all the features of severe virus-like hepatiti with some degree of pre-existing fibrosis, but no definite cirrhosis. In every other case, cirrhosis was present with characteristic hepatocytic changes and the presence and pattern of copper and copper-associated protein staining, which are distinctive features. These are unlike the changes observed in fulminant or subacute hepatitis due to viruses or other causes. Examination of the resected liver will allow a diagnosis to be made in the rare cases not identified before transplantation. This should lead to the screening of any potentially affected siblings.

OLT is the only effective treatment for FHF and end-stage chronic liver disease secondary to Wilson's disease. If untreated the condition is rapidly progressive and ultimately fatal. When progression of disease is slow and the diagnosis established before irreversible pathological changes have taken place, D-penicillamine is effective in controlling progression[7,10]. Other agents such as triene[11] and elemental zinc[12] have been recommended in place of D-penicillamine, but there is no evidence that these are more effective in patients with severe liver damage. In those presenting with FHF, medical therapy is generally ineffective and the mortality rate approaches 100 per cent[13,14]. OLT is the only effective treatment for this group of patients. Candidates for liver transplantation in Wilson's disease include[1]: patients who present with a clinical picture of FHF; young patients with cirrhosis and laboratory findings of severe hepatic decompensation who fail to improve after 2–3 months of adequate chelation therapy; and those with hepatic decompensation after discontinuation of chelation therapy.

OLT corrects the underlying metabolic abnormalities of Wilson's disease[15]. Chelation therapy is not necessary after nsplantation as the transplanted liver excretes excessive pper into the bile with clearance of free copper from the um. The neurological manifestations of Wilson's disease ve been reported to abate after liver transplantation[15]. This o occurred in the single patient with neurological manifest- ons in the present series, in whom these features resolved 3 nths after transplantation. The results of OLT in the nagement of hepatic complications of Wilson's disease in s series are encouraging. The overall survival rate is per cent and in those who presented with FHF 70 per cent. ten patients with FHF had a prognostic index based on the ring of liver function tests within the fatal range[16]. The sent results are similar to those of other series, which report -year survival rate of 60 per cent for patients with FHF[17,18]. e cause of death in two patients was multiple organ failure ondary to sepsis. The frequency of overt and occult infection patients with FHF is high and it is therefore not surprising at liver transplantation with its associated invasive nitoring and immunosuppressive therapy predisposes to ere bacterial, viral and fungal infection[19].

Hepatic complications of Wilson's disease can be successfully ated by liver transplantation. Delay in performing OLT in minant Wilson's disease will reduce the chances of overall ccess, and early transfer to a liver transplant centre provides e best hope of survival.

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Superselective intra-arterial chemotherapy with mitomycin fo gallbladder cancer

A group of 27 patients with carcinoma of the gallbladder was treat by superselective intra-arterial chemotherapy with mitomycin betwe 1981 and 1990. Results were compared with those in 22 historic controls. The overall response rate to intra-arterial chemotherapy w 48 per cent. The median survival time for responders was 34 mont and for non-responders 8 months. Survival was significantly related t tumour stage in patients treated by chemotherapy ($P < 0{\cdot}001$) *an controls* ($P < 0{\cdot}01$)*; all patients with tumour extending beyond th serosa died within 4 years. The median survival period after intra-arteri chemotherapy was 14 months, compared with 4 months in controls. Th cumulative 5-year survival rates for patients treated by chemotherap and controls were not significantly different. Cessation of chemotherap was required in 16 of the 27 patients: in eight because of tumou progression, in seven after toxicity to chemotherapy and in one becaus of patient refusal. Superselective intra-arterial chemotherapy can b useful for patients with cancer restricted to the gallbladder wall bu cannot prevent tumour growth once this has extended beyond th gallbladder serosa.*

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Carcinoma of the gallbladder is the most common malignant lesion of the biliary tract, being found in 1–2 per cent of all biliary tract operations[1,2]. Gallbladder cancer is the fifth most common tumour of the gastrointestinal tract in Finland[3]. The relative rarity of the tumour, however, reduces the likelihood of preoperative diagnosis. Carcinoma of the gallbladder tends to present late, its symptoms are indistinguishable from those of gallstone disease, it metastasizes at an early stage and has a rapidly progressive clinical course. An aggressive surgical approach has therefore been recommended to improve survival[4,5]. Not all authors agree with this[6], which is understandable as 35–85 per cent of patients have widespread disease at diagnosis and tumour growth often affects organs and structures not amenable to radical resection[7,8].

The present authors started a prospective therapeutic trial in patients with hepatic cancer, carcinoma of the gallbladder or hepatic metastases of colorectal cancer in 1981 to examine the effect of superselective intra-arterial chemotherapy with mitomycin. A group of 27 patients with gallbladder cancer diagnosed at Oulu University Central Hospital was studied prospectively from 1981. This paper reports the results and compares them with those of a historical control group.

Patients and methods

During the years 1973–1990, 68 patients with histologically proven gallbladder cancer were treated at Oulu University Central Hospital. Of these 68 patients, 27 were treated during 1973–1980 and form the historical control group. Of 41 patients treated during 1981–1990, 27 received superselective intra-arterial chemotherapy.

The male:female ratio of the whole series was 10:58 and the mean(s.d.) age 68(9) years. The mean(s.d.) age of the control group was 67(9) (range 30–89) years, that of patients treated between 1981 and 1990 76(10) (range 46–89) years and that of those treated by intra-arterial chemotherapy 64(8) (range 47–81) years.

Operative treatment in the historical control group consisted of major hepatic resection in two patients, cholecystectomy with resection of the main bile duct in three, cholecystectomy only in ten, a bypass procedure in one and exploratory laparotomy in nine. Two patients underwent biopsy only under ultrasonographic control. Three patients of this group received systemic chemotherapy with 5-fluorouracil (5-FU) and two had external radiotherapy; these patients were excluded.

Of the 41 patients treated during 1981–1990, 14 did not recei intra-arterial chemotherapy because of poor general condition an advanced disease suggesting a short life-expectancy. Operati treatment in these consisted of cholecystectomy in four patients, bypa in three, exploratory laparotomy in four and biopsy under ultra sonographic control in three. All remaining patients were eligible f intra-arterial chemotherapy; one underwent major hepatic resectio four had cholecystectomy and resection of the main bile duct, 1 underwent only cholecystectomy and five had biopsy unde ultrasonographic control.

Cholecystectomy was performed for acute cholecystitis in si patients of the control group and 14 of those receiving chemotherap In all of these cases occult gallbladder cancer was detected b histological examination.

Carcinoma of the gallbladder was staged according to Nevin *et al.*[5] stage I, intramucosal tumour; stage II, tumour in the submucosa wit invasion into the muscularis; stage III, tumour involvement of th serosa; stage IV, tumour growing into the serosa and spreading t cystic lymph nodes; and stage V, tumour extension into liver or othe organs. Staging was based on surgical findings and histologica examination in 42 patients and on computed tomography (CT) and/o ultrasonographic findings in seven (*Table 1*). All seven patients no undergoing operation had stage V disease.

Selective coeliac axis and superior mesenteric angiography wa always performed before chemotherapy. Mitomycin (20 mg diluted i 200 ml 0·15 mol/l saline) was then infused selectively into the commo hepatic artery over a 30-min period. The infusion dose was divide into two and half was injected into each artery feeding the tumour are if angiography revealed an accessory right hepatic artery originatin from the superior mesenteric artery or left hepatic artery from the le gastric artery. Selective catheterization and infusion of 10–15 m mitomycin was repeated at 6-week intervals. Chemotherapy was give in five to seven courses to a total dose of 75–85 mg. Infusions wer discontinued if toxic reactions or tumour progression precluded furthe chemotherapy.

Table 1 *Staging of carcinoma of the gallbladder*

	Stage				
	I	II	III	IV	V
Intra-arterial chemotherapy group ($n = 27$)	2	5	8	2	1
Historical control group ($n = 22$)	2	1	4	3	1

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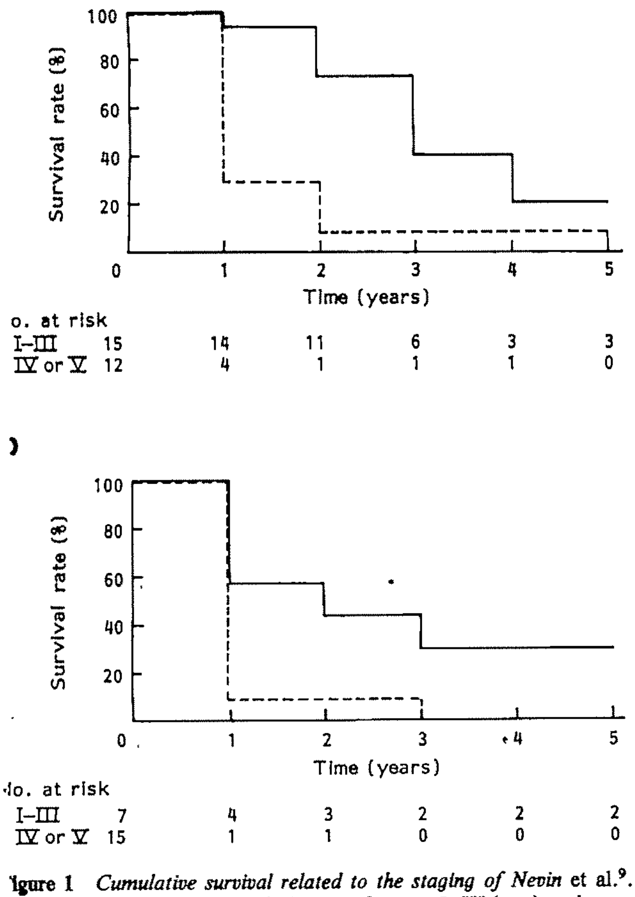
The response to chemotherapy was studied by ultrasonography and i' before each infusion of mitomycin. Response was defined according World Health Organization criteria as complete if there was total appearance of all lesions and as partial if there was a decrease of total bulk of all lesions by at least 50 per cent.

The effect of the presence or absence of various risk factors (stage or V disease, clinical jaundice, ascites, serum bilirubin level 50 μmol/l, alkaline phosphatase level >240 units/l) on the median rvival time was evaluated using the Mann–Whitney *U* test. Clinical ndice was caused by tumour invasion in ten patients and gallstone ease in three. Survival was measured from the time of diagnosis, all tients being followed until the end of February 1992 or until death. rvival curves were calculated using the life-table method[10]; the ference between survival curves was evaluated using the log rank t. $P < 0{\cdot}05$ was considered significant.

esults

mplete clearance of the tumour was achieved in six patients surgery. Of the seven patients with residual tumour, three d a complete response and four a partial response. This gave overall response rate of 13 of 27. The median survival time r responders was 34 months and for non-responders 8 months.

Patients with no risk factors who received intra-arterial emotherapy survived a median of 30 months; those with one more risk factors survived a median of 8 months. In the storical control group the median survival time was 13 months ith no risk factors and 5 months with one or more. All patients ith ascites died within 5 months, all jaundiced patients ccumbed within 8 months and all but one of those with patic spread of cancer died within 1 year. The median length survival after chemotherapy was 7 months for patients with raised alkaline phosphatase level and 16 months for those ith a high serum bilirubin concentration, the figure for the control group being 4 months in both cases. None of these differences was significant.



igure 1 *Cumulative survival related to the staging of Nevin* et al.[9]. *Survival rate in patients with disease of stages I–III* (——) *and stage V or V* (---) *after chemotherapy.* $P < 0{\cdot}001$ (*log rank test*). **b** *Survival ate in historical control patients with disease of stages I–III* (——) *and tage IV or V* (---). $P < 0{\cdot}01$ (*log rank test*)

Table 2 *Survival of patients with carcinoma of the gallbladder*

	Survival rate (%)			Median survival time (months)
	1 year	2 years	5 years	
Intra-arterial chemotherapy group ($n = 27$)	63	48	11	14
Historical control group ($n = 22$)	18	14	9	5

Table 3 *Problems with chemotherapy and causes of cessation*

	No. of patients	No. of cessations
Progression of disease	8	8
Gastrointestinal toxicity	7	5
Nephrotoxicity	2	1
Myelotoxicity	2	1
Refusal of therapy	1	1
Total	20	16

Survival was better in patients with localized tumours (stages I–III) than in those with advanced disease (stage IV or V), both in patients treated by chemotherapy ($P < 0{\cdot}001$) and in controls ($P < 0{\cdot}01$) (*Figure 1*). Cumulative survival rates for patients receiving chemotherapy and controls were 63 and 18 per cent at 1 year, and 11 and 9 per cent at 5 years respectively (*Table 2*).

The cumulative 5-year survival rate for patients with a tumour limited to the gallbladder (stages I–III) did not differ significantly between patients treated by chemotherapy and the control group (*Figure 1*). The median survival time after chemotherapy was 32 months and in the historical control group 14 months.

All patients with tumours extending beyond the serosa died within 4 years, cumulative survival rates being 37 per cent at 1 year and 14 per cent at 2 years after chemotherapy, compared with 9 per cent and nil in controls. These rates were not significantly different. The median survival times were 8 and 3 months respectively.

Chemotherapy had to be discontinued in 16 of the 27 patients. The most frequent causes of cessation were progression of tumour growth (eight patients) and gastrointestinal toxicity (five) (*Table 3*). This toxicity included gastric ulcers in five patients and diarrhoea with vomiting in two. Two patients developed leukopenia and two had raised serum creatinine values. Of the 11 patients who received a full course of therapy, eight are still alive with a median survival time of 38 months.

Discussion

Carcinoma of the gallbladder is a discouraging disease with a poor prognosis. There is considerable difficulty in establishing the diagnosis before operation[11] and 10–20 per cent of carcinomas are first detected when the pathologist examines the excised gallbladder[12,13]. If the incidentally diagnosed carcinoma is restricted to the mucosa or muscularis, cholecystectomy alone is generally effective[14]. Shieh *et al.*[15] reported a 5-year survival rate of 66·5 per cent for patients with tumours confined to the gallbladder wall. Extended cholecystectomy has been recommended, however, even for patients with tumours superficial to the subserosa, as patients so treated have survived longer than those undergoing simple gallbladder removal[16].

When the present authors' results with hepatic artery ligation and regional intra-arterial chemotherapy using 5-FU for hepatic tumours proved unsatisfactory[17,18], a new prospective treatment trial was started using mitomycin as the antineoplastic agent in selective intra-arterial infusion. Preliminary results using intra-arterial chemotherapy were promising, with an overall response rate of three of five patients with gallbladder cancer[19]. Mitomycin was chosen because it is claimed that hepatic tumours are responsive to it[20,21] and the agent can be used at 6-week intervals. It also has potential advantages such as preferential activation of cytotoxic metabolites by hypoxic cells[22] and entry into the enterohepatic circulation[23].

The response rate to combined surgery and superselective intra-arterial chemotherapy was 48 per cent. Watkins and Khazei[24] reported a response to intra-arterial 5-FU or floxuridine in half of their patients and Perpetuo *et al.*[25] found a partial reduction in the size of tumours in three of five patients receiving 5-FU and nitrosoureas or doxorubicin. Hall *et al.*[26] used a regimen of doxorubicin, carmustine and ftorafur for patients with gallbladder and biliary tract cancer; they obtained a response in 43 per cent, with a median survival time of 11 months for those responding. Smith *et al.*[27] reported a response rate of 63 per cent to hepatic artery infusion of 5-FU and mitomycin. They treated 11 patients with histologically proven cholangiocarcinoma and gallbladder cancer, the latter surviving a median of 12·5 months. The median survival period of responders in the present series was 34 months, largely the result of selection of patients with a favourable Nevin stage.

Ascites and hepatic spread of disease are features of dissemination. Patients with simultaneous acute cholecystitis and carcinoma of the gallbladder may have a resectable tumour even in the presence of a raised alkaline phosphatase or serum bilirubin level and even jaundice. This makes the use of these risk factors alone inappropriate for the evaluation and prognosis of gallbladder cancer.

Tumour stage and grade are predictive of outcome[28,29]. Tumours in stages I–III, which are limited to the gallbladder wall, were associated with a more favourable outcome in the present study, but there was no difference in outcome between patients receiving intra-arterial chemotherapy and historical controls. Patients with cancer growth outside the gallbladder serosa did not survive longer than 4 years even after chemotherapy.

However, median survival times were longer after mitomycin infusion both in patients with tumour confined to the gallbladder wall and in those in whom tumour extended beyond the serosa than in those who did not have chemotherapy. Nevertheless, overall long-term survival was not affected, which suggests that this prolongation of median survival time could be at least partly a reflection of patient selection for chemotherapy.

An increased median survival time after intra-arterial chemotherapy is consistent with the observations of Treadwell and Hardin[30], who found prolonged survival in patients receiving adjunctive chemotherapy. In a series of 112 patients with gallbladder cancer, survival was improved to a modest but significant degree in those treated with surgery plus adjuvant chemotherapy[31]. A prolonged survival over historical controls has also been documented by von Eyben *et al.*[32], who used mitomycin intra-arterially in advanced gallbladder cancer. The experience of the Eastern Cooperative Oncology Group was discouraging, however, when patients with advanced gallbladder or bile duct cancer were treated with cytotoxic agents, and none of the regimens studied was recommended for clinical practice[33]. According to their Roswell Park experience, Silk *et al.*[34] believe that the evidence for a possible benefit from chemotherapy is too weak to serve as the basis for treatment outside clinical trials, because any benefit can be attributed to patient selection. We partly agree with this. In the present study, there was no convincing evidence that mitomycin has any significant clinical effect when administered by superselective infusion at 6-week intervals.

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ase report

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erniation at the site of cannula ısertion after laparoscopic holecystectomy

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aparoscopic cholecystectomy has revolutionized the surgery gallbladder disease. With any new procedure, careful aluation of morbidity and mortality is necessary; major and inor complications of laparoscopic cholecystectomy have en reported[1–5]. This paper describes a dangerous compli- tion that led to reoperation within the first week and gnificantly increased hospital stay.

ase report

71-year-old woman with symptomatic gallstones was admitted for ective laparoscopic cholecystectomy. Previous surgery included only wer quadrant gynaecological procedures. Cholecystectomy was rried out using four cannulas and the stone-filled gallbladder removed the epigastric port (10-mm cannula) without extension of the wound. ll carbon dioxide was expelled before extraction of the final bumbilical cannula. A few adhesions were noted in the lower domen.

Initial postoperative recovery was uneventful and the patient began light diet on the first day. However, she began to vomit bile-stained uid on the second day and the following day was noted to have a nall firm swelling deep to the umbilical wound. This was initially ought to be a wound haematoma and was treated expectantly. The atient developed signs of small bowel obstruction and continued to omit bile-stained fluid, but had no pain. On the sixth day after peration the subumbilical wound was explored. A Richter-type hernia as found with ischaemia of the small bowel; resection with primary nastomosis was performed. Postoperative recovery was uneventful. istological analysis of the resected specimen confirmed a 9-cm length f deeply congested small bowel with foci of recent haemorrhagic ansmural infarction. Resection margins were viable.

Discussion

Complications of laparoscopic cholecystectomy continue to be reported. These have been principally bile duct injury, haemorrhage from the gallbladder bed or cystic artery, bile leaks and retained stones[1–5]. A number of reports have documented an increased incidence of wound infection, especially of the subumbilical wound, the usual exit site for the gallbladder[1,3]. Little attention has been paid to the method of wound closure. Fascial suturing is not performed routinely by many surgeons and the need for fascial closure remains controversial[1,2]. Hernia at the insertion site of laparoscopic cannulas has been described before, but no acute sequelae resulted[2]. One case of small bowel obstruction has been described, but was secondary to inadvertent suturing of small bowel serosa to the anterior abdominal wall[5]. The peritoneal surface of the wound should be visualized before removal of the cannula to confirm the absence of adherent bowel. It is difficult to visualize this aspect when suturing the wound after withdrawal of the final cannula.

This is believed to be the first reported instance of this complication. It illustrates the need for careful fascial closure of all 10-mm wounds whether the gallbladder has been removed through them or not and whether they have been extended or not. Any unexplained swelling should be considered a hernia until proven otherwise. The presence of adhesions in the lower abdomen as a predisposing factor in the development of this hernia is unclear.

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Sclerotherapy of the human gallbladder using ethanol and tetracycline hydrochloride

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Dissolution therapy, lithotripsy and percutaneous cholecystolithotomy[1] have all been suggested as alternatives to cholecystectomy for the management of symptomatic cholelithiasis. Despite their theoretical and practical advantages, these conservative methods suffer from limited applicability and high recurrence rates.

Recurrence of gallstones might be minimized if bile could be prevented from entering the gallbladder and if its mucosa could be destroyed by sclerotherapy. In animals, sclerosants such as heated 60 per cent diatrizoate meglumine and absolute alcohol instilled into the gallbladder after occlusion of the cystic duct induce transmural fibrosis[2].

Tetracycline solution (pH 2·0) is irritant to tissues and has been used in the treatment of malignant pleural effusion, in sclerosing recurrent thyroid cysts and, more recently, for the obliteration of chronic biliary–cutaneous fistula[3].

For some time the author has been performing cholecystectomy under local anaesthesia in high-risk patients. Sclerotherapy of the gallbladder was developed for cases in which obscure local anatomy rendered dissection unsafe.

Patients and methods

Patients were selected for cholecystolithotomy and sclerotherapy as described above. Relevant clinical problems included post-tubercular pulmonary fibrosis, portal hypertension related to schistosomiasis, chronic obstructive airway disease, advanced cardiac disease, anticoagulant therapy, extreme old age and pregnancy. Each patient had two or more of these clinical problems. No patient had jaundice, acute cholecystitis or ultrasonographic evidence of bile duct stones or obstruction.

Preoperative preparation included the administration of ceftriaxone, metclopramide to alleviate nausea during manipulation of the gallbladder, and pethidine for analgesia. A nasogastric tube was also inserted. Diazepam was given intravenously during the procedure.

The abdominal wall was infiltrated with 0·5 per cent lignocaine along the upper part of the lateral border of the right rectus muscle and along the line of incision. A short right upper paramedian incision was used; the rectus muscle was split vertically. The cystic duct was isolated and ligated in continuity. The gallbladder fundus was opened, calculi were removed and the lumen was washed with saline. Accessory ducts were sought and sutured with catgut. The gallbladder was filled with absolute alcohol for 3 min; the mucosa was then rubbed with gauze. Finally, 2 ml tetracycline hydrochloride solution (50 mg/ml) was instilled into the lumen and the cholecystostomy was closed.

The patient returned to the ward soon after, the nasogastric tube was removed and oral liquids were allowed. Solid diet was resumed on the first day after operation.

Results

During the period 1989–1991, 20 patients with uncomplicated cholelithiasis (16 women, four men; mean age 56 (range 35–93) years) were treated by cholecystolithotomy and sclerotherapy. There were no perioperative deaths and no patient requir blood transfusion. No major complications were encounter and 15 of the patients were discharged by day 3 after operatio

Patients have been followed for 1–3 years. Thirteen report a complete cure of symptoms while five were improved. Th patients died from unrelated illness during the follow-up peri Postoperative ultrasonography revealed the following sequ tial changes: (1) increased haziness of the outline of gallbladder with a surrounding hyperechoic halo, suggestive an inflammatory reaction; (2) progressive shrinkage of gallbladder lumen with thickening of the wall. No case mucocele formation has been detected; (3) complete obliterati of the gallbladder in six patients; and (4) recurrent or resid stone in one case. This stone, trapped in a closed fibrous cav (*Figure 1*), has been asymptomatic.

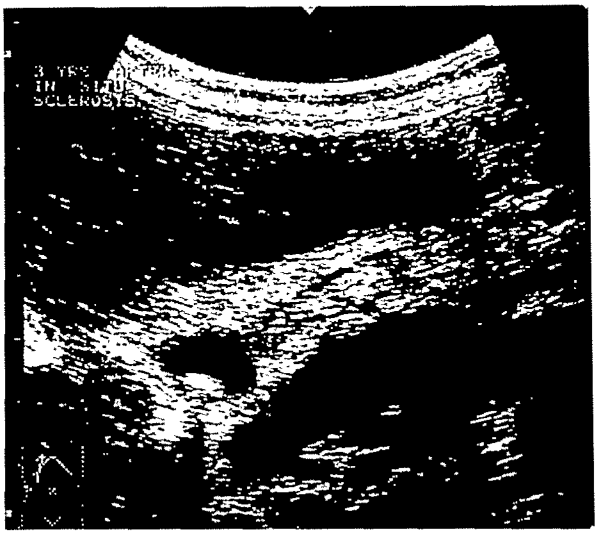

Figure 1 *Ultrasonogram of a sclerosed gallbladder after treatment ethanol and tetracycline hydrochloride. A recurrent calculus can be trapped in the fibrosed Hartmann's pouch. The patient rem asymptomatic*

Discussion

The present study has shown that chemical sclerosis of t human gallbladder after cystic duct ligation is safe and effecti in minimizing gallstone recurrence. Sclerosant chemothera may have wider application in the management of uncomplicat cholelithiasis. Perhaps the greatest potential lies in its possib combination with percutaneous extraction of gallstone However, the procedure described here may be performed safe with minimal risks under local anaesthesia. It requires sophisticated equipment, incurs no high expenditure and c readily be undertaken by the general surgeon in a bas operating theatre. The composition and number of calculi an the patency of the cystic duct impose no constraints on th selection of patients.

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Prophylactic use of cefuroxime in biliary tract surgery: randomized controlled trial of single *versus* multiple dose in high-risk patients

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To assess the efficacy of a single-dose short-acting antibiotic in the prevention of septic complications after biliary surgery, a randomized controlled double-blind multicentre trial was conducted. One dose of cefuroxime before operation (1·5 g intravenously) was compared with a three-dose regimen of the drug as control (1·5 g before and two doses of 0·75 g after operation). The study group comprised 1004 patients with risk factors for infection, who were followed for 4–6 weeks after surgery. The characteristics of both treatment groups were comparable. No significant difference was found between the one- and three-dose antibiotic regimens in preventing postoperative wound infection: 6·6 versus *6·2 per cent for minor wound infection (*P = *0·78) and 4·6* versus *3·8 per cent for major wound infection (*P = *0·52). The estimated difference in major wound infection rate between the two groups was 0·8 per cent (95 per cent confidence interval −1·7 to 3·3 per cent).*

iliary tract surgery is a popular area for study of single-dose tibiotic regimens. In placebo-controlled trials in which atients received a single dose of cephazolin, cefuroxime, famandole, cefotaxime, gentamicin or co-trimoxazole, the eated groups showed lower rates of postoperative wound fection[1–10]. In comparative trials, single doses of cefotaxime, fotetan, ceftriaxone and moxalactam were as effective as ultiple-dose cephazolin or cefoxitin[11–15]. In spite of much fort, the duration of antibiotic prophylaxis remains a subject r debate[16].

A randomized controlled double-blind multicentre trial of ngle *versus* multiple dosage of cefuroxime was conducted in atients undergoing biliary surgery who had risk factors for fection. As the value of antibiotic prophylaxis in high-risk liary surgery is now well established, it was considered nethical to use a placebo or no-treatment control group. efuroxime, a second-generation cephalosporin with an imination half-life <1·5 h, was chosen because it is considered be a suitable antimicrobial drug for prophylaxis in surgery volving the gastrointestinal tract above the caecum[17–21].

atients and methods

atient population

atients were enrolled between February 1987 and May 1990 at 14 utch hospitals (the Galant Trial Study Group). Ethical committee pproval was obtained from each participating centre. All patients heduled for biliary tract surgery were eligible if they presented with least one of the risk factors shown in *Table 1*. These factors are sociated with an increased risk of positive bile culture[22–25]. Patients ere not eligible if they met one of the following exclusion criteria: llergy to cephalosporins, haemodynamic instability, severe renal sufficiency (creatinine level >300 μmol/l), pregnancy or lactation, ntibiotic therapy within 1 week before operation, immunosuppressive erapy, concomitant intra-abdominal procedures such as appendictomy or gastric resection, and resection of the common bile duct BD) (Whipple's procedure).

reatment regimens, randomization and blinding

ll study patients received 1·5 g cefuroxime as a rapid intravenous fusion at the time of induction. Subsequently, at 8 and 16 h after peration, patients received either 0·75 g cefuroxime intravenously mixed in 100 ml saline with riboflavin; group 2) or an intravenous placebo (100 ml saline with riboflavin; group 1). Postoperative cefuroxime or placebo of identical appearance was supplied by the relevant hospital pharmacy in identical vials.

Randomization was accomplished by computer-generated sheets retained in the hospital pharmacies. At each centre, patients eligible for the study were randomly assigned individually, in blocks of ten, to receive a single or multiple dosage of cefuroxime. To minimize the effect of different operation techniques on the results, cholecystectomy was standardized as much as possible, but violation of the standard was not considered a reason for withdrawal from the trial.

Definitions

Wound infection was graded as follows: 0, no sign of infection; 1, minor infection (erythema, stitch abscess or skin edge necrosis); and 2, major infection (purulent discharge or wound dehiscence). Pus could be detected within a few days of operation (in-hospital wound infection) or its appearance could be delayed for as long as 3 weeks (delayed wound infection).

Wound dehiscence was a dehiscence of cutis and subcutis over at least 5 cm.

Bacteraemia was defined as a positive blood culture and/or chill with rectal temperature >39°C or axillary temperature >38·5°C.

Urinary tract infection was an otherwise unexplained fever with local symptoms of urinary tract infection and/or positive urine culture.

Pneumonia was defined as purulent sputum or otherwise unexplained pulmonary infiltrate and either fever or respiratory symptoms.

Table 1 *Distribution of risk factors in 1004 eligible patients*

	No. of patients		
	Group 1 ($n = 501$)	Group 2 ($n = 503$)	P*
Age ⩾60 years	417 (83·2)	406 (80·7)	0·30
Jaundice (bilirubin level ⩾50 μmol/l)	51 (10·2)	36 (7·2)	0·09
Acute attack of cholecystitis within 1 month before operation	156 (31·1)	159 (31·6)	0·87
Common bile duct stones	73 (14·6)	53 (10·5)	0·06
Previous biliary tract surgery	10 (2·0)	13 (2·6)	0·53
Chill or fever within 1 week before operation	18 (3·6)	12 (2·4)	0·26

Values in parentheses are percentages. *χ^2 test

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Acute cholecystitis was defined as acute abdominal pain for >24 h but <1 week, with tenderness in the right upper abdomen and/or palpable gallbladder, leucocytosis $>10 \times 10^9$/l and/or rectal temperature >38°C, or axillary temperature >37·5°C and, optionally, proven gallstones or pathological hepatic iminodiacetic acid (HIDA) scintigraphy.

Surveillance of postoperative infection

Wounds were assessed on days 5 and 10 after operation or on the day before discharge from hospital. In addition, all patients were reviewed in the outpatient department 4–6 weeks after discharge to detect any evidence of late sepsis. Wounds and drain sites were inspected by the surgeon or resident responsible for postoperative patient care. In cases of unexplained fever, radiological and bacteriological assessments of possible respiratory or urinary tract infection were made during follow-up. All data were recorded on specially designed study forms.

Bacteriological assessment

Samples of gallbladder bile were aspirated aseptically during operation and sent to the laboratory in a syringe with a rubber stopper on the needle. Deep wound swabs were obtained after closure of the abdominal cavity, and other wound swabs were taken in the postoperative period in the event of wound drainage. All material was dispatched to the bacteriology department immediately, or stored in transport medium for later culture. Specimens were cultured aerobically and anaerobically. The media for aerobic cultures were 5 per cent sheep blood, chocolate, MacConkey and phenylethanol agar. For anaerobic culture, specimens were plated on to anaerobic sheep blood agar and sheep blood agar with vancomycin, colistin and nystatin, and incubated in an anaerobic tent. Aerobic plates were examined after 24, 48 and 72 h for bacterial growth, anaerobic plates at 48 and 72 h.

Number of patients

Calculation of the sample size was based on the following three assumptions: (1) that grade 2 wound infection would occur in 5 per cent of the multiple-dose treatment group; (2) that detection of at least 5 per cent more major infections was necessary in the single-dose treatment group; and (3) that the detection of a significant difference of between 5 and 10 per cent major wound infections has a power of 80 per cent. Power calculations led to the conclusion that approximately 1000 patients (500 in each trial arm) were necessary. Testing was based on a significance level (α) of 0·05 (two-sided).

Withdrawals

A sufficient number of patients were randomized to ensure that 1000 would meet the criteria for evaluation. Patients were withdrawn from analysis if they did not meet one of the inclusion criteria, if they met one of the exclusion criteria, if no eligible procedure was performed (e.g. operation for irresectable carcinoma) or if postoperative follow-up was impossible. If the study medication was inadvertently omitted or another antibiotic given, the patient was included in the analysis on an intention to treat basis.

Statistical analysis

Percentages and two-way tables were analysed using the χ^2 test. For 2×2 tables with small expected frequencies, Fisher's exact test was used. If relevant, a 95 per cent confidence interval was calculated for the difference of two percentages. Approximately continuous data were assessed using the Mann–Whitney *U* test.

Results

Patient population

A total of 1077 patients were randomly assigned to receive either one or three doses of cefuroxime. The risk factors for infection in the 1004 patients analysed are listed in *Table 1*; 73 patients were withdrawn from analysis for the reasons shown in *Table 2* (two major wound infections developed in this group).

Characteristics of the 1004 patients are shown in *Table 3*. There were no important differences between the two groups with regard to the variables shown or any other parameters evaluated. Only a previous gastric resection showed a significantly higher incidence in the multiple-dose treatment group.

Cholecystectomy was performed through a right subcostal incision in 90·2 per cent of patients. CBD exploration was planned in 126 patients, but ultimately performed in 2 (20·6 per cent). Opening of the CBD, with or witho choledochoscopy, revealed duct stones in only 55·6 per cent patients.

Protocol violations

Several minor protocol violations to the standardized techniq of cholecystectomy were noted. The most frequent modificati was closure of the skin with traumatic sutures (20·7 per cent None of the protocol violations showed a significantly differe frequency between the two groups nor a significant effect the development of major wound infections.

Bacteriological assessment

Bile culture specimens were obtained from 934 patien (93·0 per cent). Overall, cultures were positive in 3 (34·6 per cent) of these patients, ranging from 38·1 100 per cent for the various risk factors. The predomina aerobic organisms (*Table 4*) were *Escherichia coli* (1 isolates), streptococci (111), *Klebsiella* sp. (71) and staphyl cocci (17). The predominant anaerobic bacteria we *Clostridium* (33 isolates, including 28 of *C. perfringen* and *Bacteroides* sp. (15 isolates, including eight of *fragilis*). Polymicrobial colonization was present in 115 cas (35·6 per cent).

Postoperative infection

Follow-up evaluation on days 5 and 10 (or the day befo discharge from hospital) and at 4–6 weeks after surgery w

Table 2 *Reasons for withdrawal of 73 patients from analysis af randomization*

	No. of patients*	
	Group 1	Group
No inclusion criterion present	10	7
Another antibiotic given within 1 week before surgery	6	9
Incomplete follow-up after surgery	5	3
Patient died before completion of follow-up	4	1
No biliary operation performed	7	3
Concomitant disqualifying procedure performed, including Whipple's operation	5	4
Immunosuppressive medication at time of operation	4	2
Haemodynamic instability of patient at operation	0	3
Total	41	32†

*In six patients the study medication was inadvertently omitted; th are included in the analysis on an intention to treat basis. †$P >$ 0·0

Table 3 *Characteristics of the 1004 patients studied*

	Group 1 (n = 501)	Group 2 (n = 503)	P
No. of women	344 (68·7)	346 (68·8)	0·9
Age (years)*	66·0(11·8)	64·7(12·4)	0·0
Body mass index (kg/m^2)*†	25·9(3·9)	26·4(4·0)	0·1
Acute cholecystitis	109 (21·8)	113 (22·5)	0·7
Acute admission to hospital	184 (36·7)	191 (38·0)	0·6
Emergency operation	33 (6·6)	42 (8·3)	0·2
Preoperative length of stay >1 day	160 (31·9)	161 (32·0)	0·9
Diabetes mellitus	44 (8·8)	31 (6·2)	0·1
Cardiovascular disease	176 (35·1)	171 (34·0)	0·7
Chronic respiratory disease	35 (7·0)	39 (7·8)	0·6
Previous gastric resection	23 (4·6)	40 (8·0)	0·0

*Values are mean(s.d.); other values in parentheses are percentage
†Calculated as weight (kg)/height^2 (m^2)

ble 4 *Organisms isolated from positive cultures of 323 bile specimens, 1 peroperative wound swabs and 26 postoperative wound exudates*

	No. of isolates		
		Wound	
	Bile (*n* = 323)	Peroperative (*n* = 221)	Postoperative (*n* = 26)
robic			
Gram-positive			
Streptococci	111 (34·4)	43 (19·5)	9 (35)
Staphylococci	17 (5·3)	66 (29·9)	10 (38)
Gram-negative			
Escherichia coli	187 (57·9)	65 (29·4)	16 (62)
Klebsiella	71 (22·0)	19 (8·6)	3 (12)
Enterobacter	16 (5·0)	7 (3·2)	2 (8)
Proteus	12 (3·7)	3 (1·4)	1 (4)
Pseudomonas	1 (0·3)	3 (1·4)	0 (0)
aerobic			
Gram-positive			
Clostridium	33 (10·2)	6 (2·7)	0 (0)
Streptococci	5 (1·5)	2 (0·9)	0 (0)
Gram-negative			
Bacteroides	15 (4·6)	4 (1·8)	0 (0)
her organisms	41 (12·7)	52 (23·5)	4 (15)
tal	509	270	45

lues in parentheses are percentages

ble 5 *Outcome*

	Group 1 (*n* = 501)	Group 2 (*n* = 503)	*P*
ound infection*			
Minor	33 (6·6)	31 (6·2)	0·78
Major	23 (4·6)	19 (3·8)	0·52
Wound dehiscence	9 (1·8)	2 (0·4)	0·04
Delayed wound infection			
Minor	6 (1·2)	8 (1·6)	0·46
Major	2 (0·4)	6 (1·2)	0·08
ther infectious complications*			
Fever†	60 (12·0)	49 (9·7)	0·26
Bacteraemia	10 (2·0)	9 (1·8)	0·80
Urinary tract infection	19 (3·8)	24 (4·8)	0·44
Pneumonia	12 (2·4)	9 (1·8)	0·50
ortality*‡			
Sepsis-related	0 (0)	0 (0)	—
Other	2 (0·4)	0 (0)	0·25
tients receiving antibiotics other than trial medication after operation*	56 (11·2)	37 (7·4)	0·04
ength of postoperative stay (days)			
Mean(s.d.)	11·8(5·4)	11·7(7·1)	0·02
Median (range)			
Uncomplicated (*n* = 899)	10 (4–49)	9 (4–45)	
Major wound infections (*n* = 42)	18 (9–44)	15 (8–48)	
Other septic complications (*n* = 192)	13 (4–41)	14 (5–72)	
Total (*n* = 1004)	10 (4–49)	10 (4–72)	

Values in parentheses are percentages. †Temperature >39°C, or 38°C for ≥4 days. ‡Five patients who died were withdrawn from e analysis

ompleted in all patients (*Table 5*). Minor wound infection was letected in 64 patients (6·4 per cent) and major wound infection n 42 (4·2 per cent) (*Table 5*). Differences between the two tudy groups were not significant. The estimated difference in najor wound infection rate between the two study groups was 8 per cent (95 per cent confidence interval −1·7 to 3 per cent). Delayed wound infection developed in 22 patients 2·2 per cent). Wound dehiscence occurred in 11 patients, nine f whom were in the single-dose group (*P* = 0·04).

Fever after surgery (>39°C and/or ≥38°C for ≥4 days) was noted in 109 patients (10·9 per cent). Fever was unexplained in 47 patients; otherwise it was related to pneumonia, urinary tract infection, bacteraemia or wound infection. The difference between the two study groups was not statistically significant.

Mortality

Five patients of mean age 70·8 (range 64–80) years died within 4 days of operation and were withdrawn from the analysis. All five had a history of cardiac disease, and in four the probable cause of death was myocardial infarction. One patient with signs of hypovolaemic shock and liver failure had massive bleeding from the liver, and liver cell necrosis was demonstrated at autopsy.

Two patients included in the analysis died, from a pulmonary embolism on day 11 and myocardial infarction on day 14.

Additional antibiotics

Additional antibiotics were used after operation in 93 patients (9·3 per cent). In 74 patients (7·4 per cent), the antibiotics were given for septic complications: 43 receiving the single-dose *versus* 31 the multiple-dose treatment (*P* = 0·12).

Adverse effects

Only one instance of urticaria was noted in the group of 1077 randomized patients. No correlation with the antibiotic therapy was suspected in the patients who died.

Discussion

The results of the present study show that one dose of a short-acting agent (half-life <1·5 h) is as effective as a three-dose regimen in preventing major wound infection after biliary tract operation. The estimated difference in the major wound infection rate between the two study groups was 0·8 per cent (95 per cent confidence interval −1·7 to 3·3 per cent). The results can best be compared with those from another multicentre study of antibiotic prophylaxis in 1451 patients with risk factors for infection who underwent gastroduodenal and biliary surgery[26]. Single-dose cefotaxime was compared with four doses of cefoxitin. Cefotaxime is also a short-acting agent, with a serum half-life of 1·2 h. The frequency of wound infections was 3·3 per cent in patients given cefotaxime and 7·6 per cent in those receiving cefoxitin. The 95 per cent confidence interval of the difference was 1·9–6·7 per cent.

In recently published trials of antibiotic prophylaxis in primary gallbladder surgery, a variety of antimicrobial agents were investigated: single-dose cefonicid *versus* single-dose mezlocillin[27], multiple-dose cefmetazole *versus* multiple-dose cefoxitin[28], single- *versus* multiple-dose cefotaxime[29], single-dose aztreonam *versus* multiple-dose gentamicin[30], single-dose ceftizoxime *versus* single-dose cephradine[31] and single-dose piperacillin *versus* single-dose tobramycin[32]. The largest group in these trials consisted of 99 patients[31]. Wound infection rates varied between 0 and 19·5 per cent. Rodolico *et al.*[29] concluded from only 44 patients that aztreonam is safe and effective for the prevention of infection following biliary surgery. Lewis *et al.*[30] validated from a total of 26 patients the efficacy of single-dose cefotaxime prophylaxis in high-risk patients undergoing gastroduodenal surgery. The conclusions drawn from these studies were premature.

Although there was no difference in wound infection rates in the present study, statistically significant differences were found between the groups in mean hospital stay, development of wound dehiscence and use of additional antibiotics in the postoperative period. Although wound dehiscence might result from technical error, a direct relationship with wound infection has previously been demonstrated. Because such factors may play a major role in a cost analysis, they should be examined more thoroughly in future trials.

It is suggested in the literature that many other factors affect normal wound healing, including body mass index, hospital stay >1 week immediately before operation, shaving of the operative site 1 day before surgery, duration of operation and wound haematoma. None of these factors showed any prognostic effect on the development of major wound infection in the present study.

It is accepted that wound infection is usually caused by biliary micro-organisms[33–35]. The drainage was cultured in 26 of 42 major wound infections, and 22 were positive. Eighteen of the 22 were associated with positive bile cultures and in 14 cases the same organism was isolated from the subcutaneous tissue as had previously been cultured from the biliary tract. The organism most commonly cultured in bile and infected wounds was *E. coli*. On the other hand, staphylococci were uncommon in bile (5·3 per cent) and relatively frequent in major wound infections (38 per cent). This finding has been reported by others[36–38]. *Staphylococcus epidermidis* was frequently grown from the subcutaneous tissues and appeared to be of pathogenic significance in five patients. Although cefuroxime is less effective against *Streptococcus faecalis*, *B. fragilis* and *Pseudomonas* spp. (< 50 per cent sensitivity), these organisms seem to play a minor role in the development of major wound infection. From the present bacteriological assessment it seems that both endogenous and exogenous contamination were causes of wound sepsis. It is concluded that the prophylactic antibiotics used should also be effective against exogenic wound contaminants.

Whether or not all patients undergoing cholecystectomy should receive antibiotic prophylaxis remains controversial. It is generally accepted that those undergoing biliary tract operation are at higher risk of developing postoperative sepsis if bacteria are present in the bile at the time of operation[33,38–41]. The incidence of bile colonization in low-risk patients lies within the range 8–19 per cent[33,40–42] and in high-risk patients 30–45 per cent[23,33,43]. Although antibiotic prophylaxis may not be essential in patients without risk factors undergoing biliary tract surgery, a beneficial effect in clean operations has been reported[44].

Finally, some comment seems merited on the recent development and rapidly growing popularity of laparoscopic cholecystectomy. The principles of prophylaxis are not changed by minimally invasive surgery. Although wound complications seem to play a minor role, there is a greater chance of intra-abdominal spillage of bile using the laparoscopic technique. As long as no better alternative has been demonstrated, antibiotic management for laparoscopic cholecystectomy should be identical to that for open cholecystectomy. A study should be mounted to examine the risk of infection in the laparoscopic operation.

Acknowledgements

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Appendix

The Galant Trial Study Group (14 Dutch hospitals) consists of Dr P. J. Breslau, Rode Kruis Hospital, The Hague, Dr W. A. H. Gelderman, Groot Ziekengasthuis, Den Bosch, Dr A. C. van der Ham, Sint Clara Hospital, Rotterdam, Dr J. M. Heslinga, Bronovo Hospital, The Hague, Dr C. M. Hoogenboom, Van Weel-Bethesda Hospital, Dirksland, Dr C. L. Koppert, Eudokia Hospital, Rotterdam, Dr H. Kuiken, Schieland Hospital, Schiedam, Dr J. K. S. Nuytinck, Sint Ignatius Hospital, Breda, Dr K. H. Ong, Hospital Rivierenland, Tiel, Dr C. H. Ruseler, Sint Franciscus Gasthuis, Rotterdam, Dr M. K. M. Salu, Zuiderziekenhuis, Rotterdam, Dr P. F. Verhagen, Sint Maartens Gasthuis, Venlo, Dr W. F. Weidema, Reinier de Graaf Gasthuis, Delft, and Dr O. J. van West, Sint Josef Hospital, Oosterhout.

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Announcement

Surgery of the Liver, Biliary System and Pancreas

The British Council are holding a course devoted to Surgery of the Liver, Biliary System and Pancreas in The Royal College of Surgeons of Edinburgh from 17 to 23 October 1993. The course is intended for discussion of complex issues with an audience composed of relatively senior specialist surgeons. Topics to be covered will include: cholelithiasis and choledocholithiasis; minimally invasive hepatobiliary surgery; transplantation of liver and pancreas; acute and chronic pancreatitis; pancreatic and periampullary cancer; hepatobiliary trauma; portal hypertension; and hepatic and biliary malignancy. The course will be directed by Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh.

Further information can be obtained from: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK.

D. C. Carter

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Randomized study of the value of laparoscopy before appendicectomy

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Two groups of 30 women with clinical signs of appendicitis we randomized to immediate appendicectomy or diagnostic laparoscop In the latter group, appendicectomy was performed if a diagnosis acute appendicitis was established or if the appendix could not visualized. Eleven patients undergoing immediate operation h unnecessary appendicectomy, compared with two having laparoscop This difference of 30 per cent (95 per cent confidence interv 11–49 per cent) was significant (P = *0·01). There was no significa difference in postoperative morbidity rate in the two groups. Diagnost laparoscopy is a useful preliminary investigation in women with clinic signs of acute appendicitis.*

No simple test is available to confirm the diagnosis of acute appendicitis in women. Removal of a normal appendix can occur in up to 50 per cent of women when laparotomy is performed after putative diagnosis of appendicitis[1–3]. Recent reports have suggested that laparoscopy might reduce the frequency of unnecessary appendicectomy[4–11].

The aim of this study was to determine whether diagnostic laparoscopy could decrease the frequency of unnecessary appendicectomy in women with clinical signs of acute appendicitis and to evaluate whether the procedure would reduce the postoperative morbidity rate when no pathology was discovered.

Patients and methods

The trial was performed in a randomized fashion and approved by the local ethical committee. Women aged 15–56 years with clinical signs of acute appendicitis were studied. Patients presenting with signs of diffuse peritonitis, with a previous diagnosis of diffuse peritonitis and those with more than two previous lower laparotomies were excluded. Between 1 January 1988 and 26 November 1991, 30 women were allocated to each of two groups, proceeding directly to appendicectomy or undergoing diagnostic laparoscopy. Patient details are given in *Table 1*. During the study period, 91 further women underwent appendicectomy but were not randomized because of exclusion criteria or because a surgeon with laparoscopic skills was not available.

Appendicectomy was performed through a transverse incision in the right iliac fossa.

Laparoscopy was performed under general anaesthesia. Appendicitis was excluded if a normal appendix could be seen throughout its length. Appendicectomy was performed when acute appendicitis was confirmed and when a diagnosis of appendicitis could not be excluded. If other abnormalities were found the appropriate treatment was given.

The postoperative stay of the two groups was compared and complications or readmissions after surgery recorded.

Fisher's exact test was used to compare the frequency of unnecessary appendicectomy in the two groups. The Mann–Whitney U test was used to evaluate differences in postoperative hospital stay. $P < 0·05$ was considered significant.

Results

Unnecessary appendicectomy was performed in 11 women proceeding straight to operation and in two undergoing laparoscopy. This difference was statistically significant ($P = 0·01$), with a therapeutic gain of 30 per cent (95 per cent confidence interval 11–49 per cent). A normal appendix was removed in 31 of the 91 women not included in the study.

The two patients having laparoscopy who had a normal appendix removed underwent surgery because the appendix was not visualized. In a further three patients the appendix w not visualized but acute appendicitis was found at op operation.

Table 1 *Patient characteristics and outcome*

	Direct operation	Laparosco
No.	30	30
Mean (range) age (years)	25·8 (15–56)	25·3 (15–
Appendicitis	19	12
Unnecessary appendicectomy performed	11	2

Table 2 *Final diagnoses in patients without appendicitis*

	Direct operation	Laparosco
Gynaecological disorders		
Salpingitis	5	10
Ruptured ovarian cyst	2	2
Torted ovarian cyst	0	1
Hydrosalpinx	1	0
Other diagnoses		
Mesenteric adenitis	1	2
Meckel's diverticulum	1	0
No abnormality found	1	3
Total	11	18

As seen in *Table 2*, most of the other diagnoses (21 of patients) were of gynaecological disorders.

Of the 11 women proceeding directly to operation in who a normal appendix was removed, four had procedures i addition to appendicectomy. Of the women undergoin laparoscopy, 18 did not have appendicitis. One patie underwent resection for torsion of an ovarian cyst. The mea (range) postoperative stays for direct operation and laparoscop were 3·2 (1–7) and 3·8 (1–8) days respectively. This differenc was not significant ($P = 0·25$).

One patient proceeding directly to operation was readmitte with a suspected abscess and recovered after antibiotic therap No complication related to laparoscopy occurred.

Discussion

The present trial confirms previous non-randomized studies[4–1 in showing that diagnostic laparoscopy can significantly reduc

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negative appendicectomy rate, although the method failed demonstrate the appendix in 17 per cent of cases, due mainly hidden inflamed appendices sealed by the omentum. In reement with other results, many women with a normal pendix were found to have gynaecological pathology to count for the clinical presentation[3,5], but an unexpectedly gh proportion of these had salpingitis. A disproportionate mber of patients with minor changes of the salpinx may have en classified as having salpingitis. The large number of such men explains why (in contrast with other results[5]) a duction in postoperative hospital stay was not demonstrated. ese patients were treated, with observation in hospital, in is department.

Only one early complication after appendicectomy was corded, but late follow-up was not performed and minor ound complications appearing after discharge may have been issed. There were no complications after laparoscopy and, in rge series, complication rates after laparoscopy seem to be uch lower than those after removal of a normal appendix[3,12].

If available, ultrasonography may further reduce the rate of necessary appendicectomy[1]. Ultrasonographic expertise is t universally available but laparoscopy can be carried out the surgeon without other specialists. Diagnostic laparoscopy gnificantly reduces the frequency of unnecessary appendictomy in women.

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Paper accepted 22 November 1992

Announcement

Association of Surgeons in Training (ASIT)

Membership of the Association is open to all trainees in every surgical specialty. Applicants should hold either the FRCS or CSIG Diploma.

The Association represents the views of members on all matters relevant to surgical training both at national and regional level and has representatives on most of the committees and boards that administer surgical training. Membership is free.

If you are not a member, please contact the Secretary, Bob Baigrie, at 7 Coverley Road, Oxford OX3 7ET, for details of membership, the Annual General Meeting and the name of your regional representative.

The next AGM will be held at St Bartholomew's Hospital on 17–18 September at the end of the Eurosurgery '93 Meeting.

R. J. Baigrie
Honorary Secretary
Association of Surgeons in Training

Br. J. Surg. 1993, Vol. 80, July,
924–927

Safety of double-stapled anastomosis in low anterior resection

Clinical leakage of the anastomosis follows low anterior resection rectal carcinoma in 5–10 per cent of patients despite standard stapli techniques. A modification of this method has obviated the need fo distal purse string. A flexible transverse stapling instrument (Roticula 55) is applied across the rectum below the tumour, and a doub staggered row of staples is inserted as a substitute for the distal pu string. End-to-end stapled anastomosis is then performed with pera insertion of a Premium CEEA stapling instrument. In 111 patients t indications for operation were colorectal carcinoma (96 patient diverticulosis (ten), megarectum (four) and ulcerative proctocoli (one). Three patients had clinical evidence of anastomotic leakage; survived. The incidence of radiological leakage on Gastrografin ener 10–12 days after operation was 9 per cent. The perioperative mortal rate was 2 per cent; all deaths were from cardiovascular causes. Lo recurrence of tumour occurred in eight patients (7 per cent) after mean follow-up of 40 months. In conclusion, double-stapled end-to-e anastomosis has made low anterior resection for rectal carcinoma safe procedure with a low mortality rate, an acceptable local recurren rate and minimal (clinical) anastomotic leakage.

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The major factor leading to complications and death following low anterior resection for rectal carcinoma is anastomotic dehiscence[1]. Leakage into the postrectal space may result in pelvic abscess, wound fistula, peritonitis and death. The rate of anastomotic leakage in major centres varies widely. In 1979, Goligher *et al.*[2] improved on their previous high leakage rate using a circular stapling instrument but still had an appreciable leak rate of 13 per cent. Fielding *et al.*[1] audited the results of 23 UK centres and found an incidence of anastomotic leakage of up to 20 per cent; defunctioning stomas were not associated with a reduced incidence of leakage. In 1983, Cohen and colleagues[3] significantly reduced anastomotic leakage in low anterior resection using a double-stapling technique and the TA55 stapling instrument (US Surgical, Norwalk, Connecticut, USA); the radiological leakage rate was not recorded, however.

The concept of intersecting staple lines is not new, the method being originally used by Nance[4] in New Orleans, Louisiana, in 1979 for gastroduodenostomy. The technique was used in the pelvis in low anterior resection by Knight and Griffen[5], and subsequently by Cohen *et al.*[3], both of whom achieved low clinical leakage rates (0–4 per cent) in small groups of patients. However, the technique has become popular only in recent years, and few studies have evaluated its use in a large number of patients. Varma *et al.*[6] reported preliminary experience with the double-stapled technique in a series of 30 patients and documented a clinical leakage rate of 7 per cent. In 1991, Moritz *et al.*[7] compared single- and double-stapling techniques in rectal anastomosis and recorded clinical anastomotic leakage rates of 8·6 and 2·8 per cent respectively. This difference was not significant but did suggest a lower leakage rate after the double-stapled procedure. More recently, Baran *et al.*[8] reviewed a series of 104 patients who underwent double stapling, reporting a clinical leakage rate of 2·8 per cent. The present prospective study evaluates the use of double-stapled anastomosis in low anterior resection.

Patients and methods

The study was conducted on 111 patients who underwent elective lo anterior resection of the rectum or rectosigmoid colon in the colorect unit at this hospital. The series was initiated in 1987 and was prospecti and consecutive. Low anastomosis was defined as that at or below t level of the peritoneal reflection, and was confirmed by the fact th the distance of the staple line from the anal verge was ≤10 cm. Duri the series three patients with tumours within 5 cm of the anal marg underwent conversion to abdominoperineal resection based on dist margin involvement confirmed by frozen section. On the day befo operation, all patients underwent standard bowel preparation usin polyethylene glycol (Klean Prep; Birex Pharmaceuticals, Dubli Ireland), and all received standard prophylaxis for deep ve thrombosis. Antibiotic prophylaxis consisted of gentamicin (80 m and metronidazole (500 mg), and was given at induction of anaesthes and twice after operation.

All procedures were carried out by the two senior authors. operation, a lower midline incision was made, a laparotomy w performed and the inferior mesenteric vein was ligated before t colorectal dissection. After mobilization of the splenic flexure, t rectum and its mesentery were mobilized completely. The anterior rect wall below the tumour was then cleared of all excess fibrous tissue an fat by close perimuscular dissection. The dissection was continued to the lateral and posterior walls of the rectum so that a short segme of rectum (approximately 2 cm) was completely denuded down to t seromuscular layer in preparation for double stapling. A linen tape w tied tightly around the rectum below the tumour or diseased segme as a substitute for a crushing clamp (which would have interfered wi double stapling), and the rectum was irrigated *per anum* using 1 per ce chlorhexidine in water. The rectum was double stapled below the line tape using a Roticulator 55 (US Surgical), with the stapling head angle at 90° to the axis of the rectum (*Figure 1*). The upper limit of t colonic resection was then selected, the proximal colon was divide and, if necessary, divided again to ensure brisk bleeding from t resection margin. The appropriate cartridge size was chosen and purse-string whip stitch of 0 polypropylene was inserted (*Figure 2* The anvil of a Premium curved EEA (CEEA) instrument (US Surgical was then inserted into the proximal colon, and the purse string w tightened around it. The CEEA cartridge with trocar in place w inserted anally and the trocar passed through the centre of the stap line or as close as possible to it (*Figure 2*). Before closure of t instrument, care was taken to avoid excessive upward traction on t

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Presented to the Association of Surgeons of Great Britain and Ireland in Jersey, UK, April 1992

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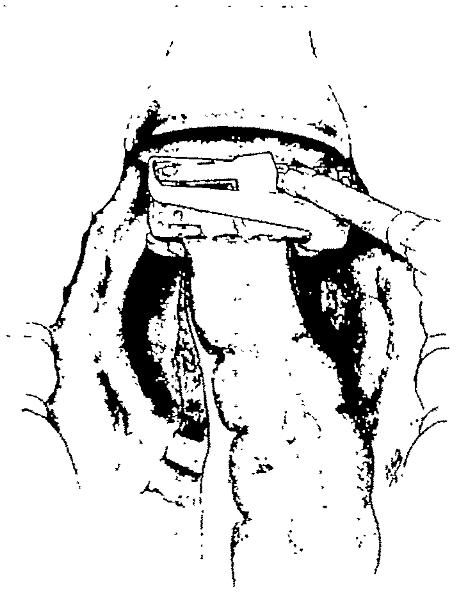
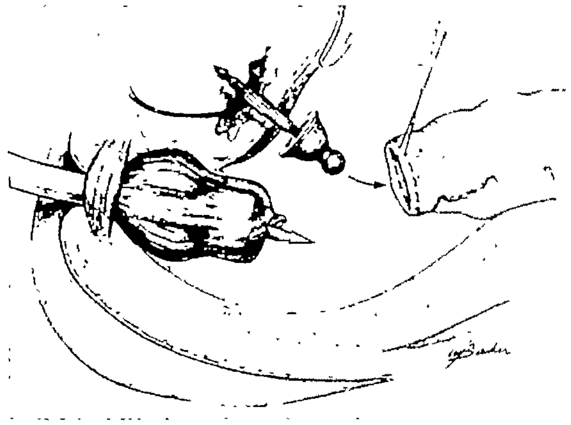


gure 1 *Placement of the Roticulator across the lower rectum. The pling head is angled at 90° to the long axis of the rectum to ensure per placement of staples. © 1974, 1980, 1988 US Surgical rporation. All rights reserved; reprinted with permission*



gure 2 *Insertion of a purse-string whip stitch and placement of the vil into the proximal colon. The CEEA cartridge is placed* per anum *th the trocar advanced through the centre of the rectal staple line. 1974, 1980, 1988 US Surgical Corporation. All rights reserved; printed with permission*

ctal stump by the perineal operator and also to avoid interposition mesorectum between the bowel ends. After closure (*Figure 3*) and ing of the Premium CEEA, the instrument was opened and two parate stay sutures of 2/0 chromic catgut were inserted into the nterior suture line to lift the anastomosis over the anvil and thus cilitate extraction of the instrument (*Figure 4*). The integrity of nastomosis was tested by air insufflation. This was performed by sertion of a rigid sigmoidoscope anally and insufflation of air into e rectum, with the top of the sigmoidoscope below the level of nastomosis. To check for air leakage, saline was poured into the odominal cavity to cover the anastomotic staple line, and the surgeon's nd was used to compress the colon above the anastomosis. The osence of bubbles indicated an air-tight anastomosis. Pelvic suction rains were placed routinely to minimize formation of pelvic ematoma.

A Gastrografin enema (Schering Health Care, Burgess Hill, UK) as administered on day 10–12 after operation to assess the diological integrity of the anastomosis[9]. Radiological leakage was efined by the demonstration of radio-opaque dye clearly visible in the rianastomotic space, with or without clinical evidence of leakage. linical leakage was defined as a breakdown in the double-stapled nastomosis resulting in clinical signs of peritonitis or septic shock such at the patient required laparotomy.

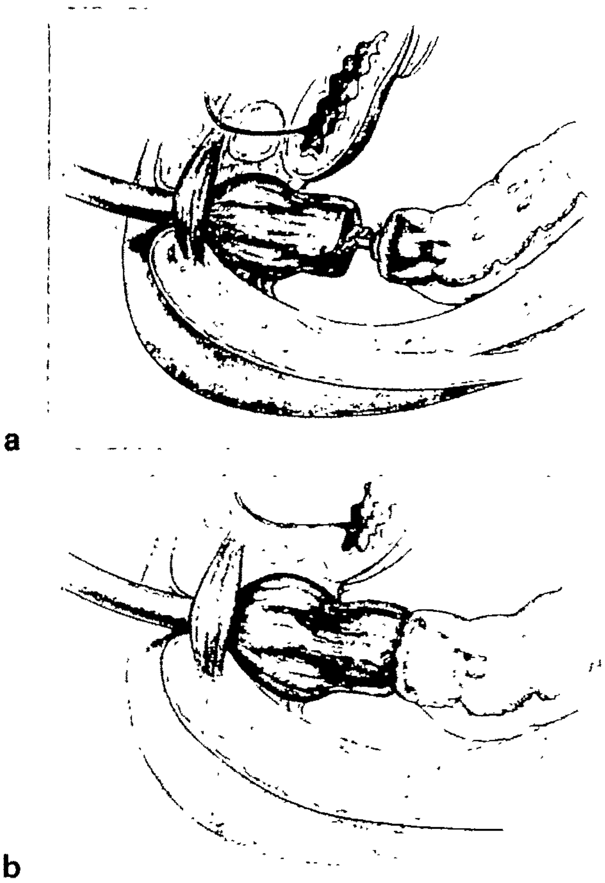


Figure 3 a *Engagement of the anvil shaft in the instrument shaft before closure;* b *closure of the CEEA instrument. It is important to ensure clearance of any redundant tissue lying between the proximal and distal bowel ends before closure. © 1974, 1980, 1988 US Surgical Corporation. All rights reserved; reprinted with permission*

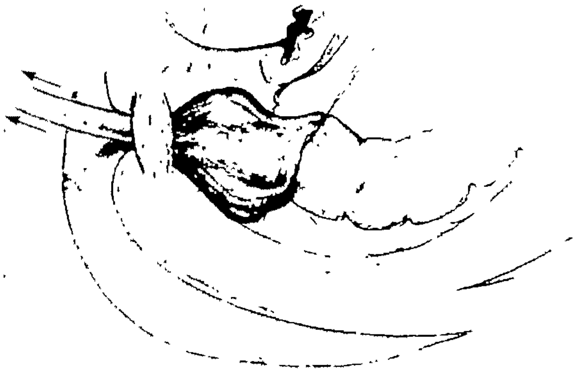


Figure 4 *After firing, two stay sutures are placed across the anterior staple line to facilitate removal of the CEEA instrument. © 1974, 1980, 1988 US Surgical Corporation. All rights reserved; reprinted with permission*

Over the past 5 years a few patients with complicated diverticular disease were treated by extended resection involving removal of the upper half of the rectum to achieve healthy distal resection margins suitable for primary anastomosis. It is not the authors' practice routinely to perform low anterior resection for diverticular disease.

Results

Of the 111 patients, 62 were men and 49 women, with an age range of 21–85 (mean 66) years. The indications for operation were colorectal carcinoma (96 patients), diverticulosis (ten), megarectum (four) and ulcerative proctocolitis (one). Rectal tumours were located at a mean distance of 9·8 (range 6–20) cm

Table 1 *Dukes' classification of colorectal tumours*

Dukes' stage	No. of patients
A	5 (5)
B	54 (56)
C	30 (31)
'D'	7 (7)
Total	96 (100)

Values in parentheses are percentages

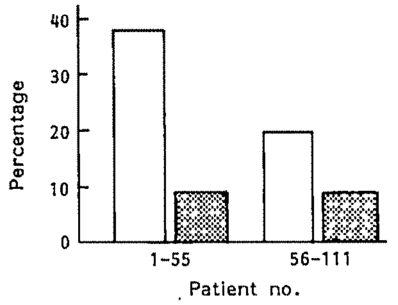


Figure 5 *Percentage of defunctioning anastomoses fashioned* (☐) versus *the proportion of radiologically defined anastomotic leaks* (▨). *Despite a halving in the number of stomas in patients 56–111, the radiological leakage rate was identical to that in patients 1–55*

Table 2 *Anastomotic complications in 111 patients*

Complication	No.
Clinical leakage	3 (2·7)
Radiological leakage	10 (9·0)
Air leakage	6 (5·4)
Clinical stricture	10 (9·0)

Values in parentheses are percentages

from the anal verge and the mean height of the rectal anastomosis above the anal verge was 5·5 (range 3–10) cm. The mean length of clearance below the tumour was 4·9 (range 2–15) cm. In the patient with a clearance of 15 cm below the tumour, a serosal tear occurred in the distal rectum during mobilization and this required resection of most of the rectum and a low anastomosis. Most patients (95 per cent) with colorectal cancer had Dukes' B or more advanced lesions at the time of diagnosis (*Table 1*).

Of the first 55 patients, 21 had a covering colostomy, but only 11 of the last 56 had a temporary stoma (*Figure 5*). The radiological leakage rate was identical (9 per cent) in both groups of patients, indicating a lack of correlation between formation of a temporary stoma and radiological leakage. Covering colostomies were performed initially as this was a new technique under scrutiny. Later in the series they were undertaken for air leakage, incomplete 'doughnuts' and inadequate bowel preparation. The mean time to colostomy closure was 13 (range 8–38) weeks.

There were three clinical anastomotic leaks (2·7 per cent) (*Table 2*), all of which occurred in men with advanced rectal tumours. The site of dehiscence was always on the posterior aspect of the anastomosis. No clinical or radiological leakage was seen at the lateral intersecting margins (so-called 'dog ear' leaks). The first clinical leak occurred in the man who had a full-thickness tear in the rectal stump secondary to traction during mobilization. The tear was recognized and repaired, and the completed anastomosis was air-tight with intact 'doughnuts', but the patient subsequently developed a clinical leak; a Gastrografin enema confirmed breakdown of the repair. T other two clinical leaks occurred after technically satisfact operations, and the anastomosis in each case was air-tight w intact 'doughnuts'.

The radiological leakage rate, as assessed by enema at 10– days, was 9·0 per cent (*Table 2*). Air leaks detected at operati occurred in 5·4 per cent of patients, and 9·0 per cent develop clinical anastomotic stricture requiring dilatation. Strict represented a real problem, symptoms of incomplete evacuati and tenesmus occurring within 6 weeks to 4 months operation. However, serial dilatation (one to three procedur was effective in every case, with no patient in the series requiri further operation. No correlation was found between rad logical or clinical leakage and subsequent stricture formati although the numbers were small.

Intraoperative technical complications occurred in 6·3 per c of cases: two rectal tears, one incomplete staple closure at lateral resection margin requiring suture, three failures disengage the anvil and one failure to disengage the cartrid The anvil was recovered by depressing the anvil button a allowing the cartridge to be removed; the anvil was then eas extracted *per anum*.

The overall mortality rate was 1·8 per cent and was confin to cardiovascular causes: one patient died from a cerebr vascular accident 30 days after operation and the other had myocardial infarction. Local recurrence of tumour has occurr in eight patients (7 per cent) after a mean follow-up of months, during which time each patient underwent rec examination and proctosigmoidoscopy at 3-monthly intervals

Discussion

A recent study by Foster and Kane[10] attempted to show th the double-stapled technique was unsafe. Double stapling w compared with purse string or suture, but doubt must be ca on the conclusion because of an insufficient number of patien in the double-stapled group. There is now good evidence in t literature to support the view that the double-stapled techniq is reliable and safe[6–8]. Moran *et al.*[11] achieved an acceptab clinical leakage rate of 9 per cent with this technique. Moreove they rejected the notion that it might lead to a higher tumo recurrence rate in the pelvis because of incorporation of tumo cells in the double-staple line. The local recurrence rate[11] w 8 per cent after a median follow-up of 32 months.

In this centre the double-stapled technique has been us for the past 5 years, employing the Roticulator to double stap the rectal stump and the Premium CEEA to construct a end-to-end intersecting stapled anastomosis. The TA55 has n been used to cross-staple the rectal stump, as the instrume does not have a flexible head and it may prove impossibl especially in the deep male pelvis, to align the devi satisfactorily across the distal rectum to ensure a vertic double-staple line.

The present study demonstrates that leakage from low rect anastomosis is primarily a technical problem. The insertion a distal purse string into the rectal stump low in the pelvis often a difficult technical manoeuvre, and double stapling the rectum overcomes this problem. Moreover, the rectal stum is not opened, thus avoiding contamination of the pelvic spac The technique also overcomes any disparity in the diameter the bowel ends, which has been a problem with the standar EEA method using a low purse string. However, care must b taken to avoid excessive denudation of the distal rectum, whic might lead to ischaemia, while too much traction on the rect stump can predispose to rectal muscle tears.

The requirement for a defunctioning colostomy i controversial. Diverting colostomy involves a two-stag procedure with a second hospital admission and the potentia for further surgical complications associated with closure[12–14] Current evidence suggests that a defunctioning colostomy ma be unnecessary in colorectal anastomosis[15,16], and Fielding *al.*[1] have suggested that a diverting stoma may be omitted whe personal leakage rate <5 per cent is achieved. The three tients in the present series who suffered clinical leaks did not ve defunctioning stomas at initial operation, but all required function subsequently. It is impossible to assess whether lack a defunctioning stoma predisposed to clinical leakage in these tients as the number with clinical leaks is too small. However, is was considered unlikely as there was no correlation between diological leakage and the use of a defunctioning stoma *igure 5*).

A low rate of clinical leakage after low anterior resection r cancer is dependent on good surgical technique[2]. In the esent study, strict attention to technical detail during double apling has minimized anastomotic leakage. First, accurate acement of the Roticulator across the rectal stump at right gles to the axis of the rectum ensures that the staples are rrectly placed. It is possible, especially with the TA55 strument, to insert the staples obliquely across the rectal wall, ading to inadequate closure. Second, excessive trimming back the mesentery and appendices epiploicae must be avoided, that the vascularity is preserved both to the rectal stump d to the proximal purse-string margin. Third, excessive ward traction on the rectal stump during insertion should avoided. Gentle counter-pressure with the top of a blunt strument (e.g. Babcock forceps) on the staple line facilitates raumatic puncture of the rectum by the trocar. It is also lieved important to relax the tension on the rectal stump fore closing the instrument, otherwise the rectum and astomotic line will recoil inwards when an attempt is made remove the cartridge, leading to difficulty in extraction and ssible damage to the staple line. Finally, as recommended the manufacturer, two stay sutures are inserted anteriorly ross the staple line to lift the anastomotic line over the edge the anvil head and facilitate removal of the instrument. If traction is still difficult despite these measures, the anvil can disengaged from its shaft by finger pressure on the anvil tton through the bowel wall. The instrument is then removed d the anvil inverted and pushed head-first through the astomosis to be removed by the perineal operator. All these ints of technique will minimize trauma to the staple lines hich, in our opinion, is the most likely cause of the high akage rates reported in some studies.

In practice, double-stapled end-to-end anastomosis in the wer rectum has been found to be superior to any former perience with the EEA stapling instrument. Before 1987, sults from this centre with the standard EEA stapling chnique were acceptable and compared favourably with those om other hospitals. In 78 cases of low anterior resection using e double purse-string technique, the clinical leakage rate was per cent, the associated mortality rate 4 per cent and the diological leakage rate 18 per cent. Subsequent use of the ouble-stapling technique at this centre had led to a fall in the clinical leakage rate to 3 per cent and a drop in the radiological leakage rate to 9 per cent. There have been no deaths associated with leakage and the rate of local recurrence has not risen, showing that the technique is safe.

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Reappraisal of radical local excision for carcinoma of the rectum

Outcome in all 167 patients treated by radical local excision for rect carcinoma between 1948 and 1984 at St Mark's Hospital was assesse in terms of the original tumour differentiation except for 15 patien with incomplete follow-up or ungraded tumours. Fifty-six of the 15 patients had low-grade tumours, with one death from carcinoma in th group. Of 81 patients with average-grade tumours, ten died fro carcinoma of the rectum: two after early reoperation and eight followin recurrence. Six of 15 patients with high-grade tumours underwent ear reoperation and three of these died from carcinoma. Among the nin patients who did not undergo early reoperation there were three relate deaths (two from carcinoma, one after rectal excision for recurrence Local excision remains a valid therapy for suitable patients wit low-grade tumours but is not recommended for those with average-grad lesions. The necessity for early reoperation in patients with high-gra tumours is questioned.

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The role of local excision in the treatment of 'early' carcinoma of the rectum is controversial. A policy for the treatment of tumours where the malignancy is in a polyp was described by Lockhart-Mummery and Dukes[1]: malignant rectal polyps could be treated by local excision if the tumour was not high grade and was fully excised to the satisfaction of both the surgeon and pathologist. These guidelines have been extended such that local excision has been used to treat pedunculated[2] and non-pedunculated[3] lesions of all grades of differentiation. Local excision is usually still reserved for patients with a pedunculated tumour or a protuberant lesion that can be made pedunculated by traction[4].

This study examined the outcome of local excision according to tumour differentiation assessed at the time of operation in 167 patients treated between 1948 and 1984. Four questions were addressed:

1. Is it safe for low-grade tumours to be treated by local excision alone provided that excision is complete?
2. Is it wise for average-grade tumours to be so treated?
3. Should all patients with high-grade tumours undergo early major reoperation?
4. Is there a place for local excision in the treatment of rectal carcinoma?

Patients and methods

The series comprised all patients treated by local excision for carcinoma of the rectum at St Mark's Hospital between 1948 and 1984 provided that the original operation was undertaken as a definitive procedure for cure, i.e. a radical operation as defined at this centre. Patients treated by local excision for palliation of symptoms were excluded. A total of 167 patients were identified: 88 men aged 29–90 (median 66) years and 79 women aged 32–90 (median 68) years.

No review of pathology was undertaken for this study because decisions as to further treatment had been based on the initial pathology report.

Characteristics that led to the original operation being a local excision are not considered in this paper. It is impossible to assess the part played by age, sex, size and location of tumour, morphology, general condition of the patient or other disease in a retrospective review. Many of these variables have been discussed elsewhere[5]. The definition of local excision as any procedure involving the removal of less than a full-thickness circumferential segment of bowel was used[4].

Follow-up

One patient, with an average-grade tumour, died after operation. S patients (one with low-grade, four with average-grade, one wi high-grade tumour), all of whom lived abroad, had inadequa follow-up of 3 months to 2 years 8 months. These seven patients an a further eight in whom the tumour was ungraded are excluded fro further analysis. The remaining 152 patients were followed for minimum of 5 years or until death.

Results

Details of outcome related to tumour grade in the 152 patien available for study are shown in *Table 1*. Early reoperatio defined as a further surgical procedure within 6 weeks of th original operation, was undertaken in a number of patients f the reasons stated below.

Low-grade tumours

Of 56 patients, three underwent early reoperation (anteri resection in each case) because of doubts relating to th completeness of excision; none had residual local tumour nodal disease. All three survived more than 5 years. Tumo recurred in two patients. One with local recurrence was treate by further local excision after 1 year and died at the age of 9 years from other causes. The other patient develope pulmonary and hepatic metastases. Six patients develope metachronous carcinoma of the large bowel.

Average-grade tumours

Of 81 patients in this group, 17 underwent early reoperation local excision in three, anterior resection in seven and excisio of the rectum in seven. There was no residual local or noda disease in 15 patients. One patient treated by anterior resectio died nearly 5 years later from carcinomatosis. One with residua

Table 1 *Overall results related to tumour grade in 152 patients*

Grade of tumour	No. of patients	No. of deaths from rectal carcinoma	No. of deaths after operation for recurrenc
Low	56	1	0
Average	81	8	2
High	15	5	1

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able 2 *Treatment of recurrence in 12 patients with average-grade mours*

rocedure	No. of patients	No. of postoperative deaths	No. of deaths from carcinoma
xcision of rectum	6	1	3
nterior resection	1	0	1
ocal excision	2	0	0
xamination under anaesthesia	1	1	0
one	2	—	2

cal tumour survived more than 5 years but another, with cal and nodal involvement, died 2 years later from carcinoma. further patient died from unrelated causes 2 years after operation. The remaining 13 survived more than 5 years.

Of the remaining 64 patients, 12 developed recurrent disease. ive had local recurrence only, three had local and nodal isease, two had nodal deposits only and two developed distant etastases. Treatment of recurrence is shown in *Table 2*.

Three patients developed metachronous tumours.

igh-grade tumours

f 15 patients in this group, six underwent early reoperation ccording to the guidelines[1] laid down in 1952 (anterior esection in one, excision of the rectum in five). No specimen howed residual local growth, although there were involved odes in four patients. Two patients with involved nodes died rom carcinoma, as did one with neither local nor nodal nvolvement. Nine patients did not undergo early reoperation. he reasons for this in two patients are unclear, but in seven here were 'mitigating circumstances', notably age, other illness r refusal of a stoma. Five of these patients survived more than years or died from unrelated causes. Four patients developed ecurrent disease (local only in three, with nodal involvement n one). Two were treated by excision of the rectum: one died fter operation and one survived more than 5 years from the econd procedure. Two patients underwent a further local xcision followed in one by radiotherapy; both died from arcinomatosis.

No patient developed a metachronous tumour within the tudy period.

iscussion

he present overall mortality rate from carcinoma and surgery or recurrence of 11 per cent (17 of 152 patients) in those with early' rectal cancer appears unacceptable. Should local excision ave any part to play in the treatment of carcinoma of the ectum? An attempt to answer this question was made by onsidering results in terms of the histological grading of the riginal tumour. This factor was a major determinant of further urgical treatment.

Excluding local excision, the proportions of low-, verage- and high-grade tumours are about 23, 59 and 18 per cent respectively in the general series of carcinoma of he rectum at St Mark's Hospital (J.K.R., unpublished results). n the present series of tumours treated by local excision, low-grade lesions accounted for 56 of 152 (37 per cent). In this group of patients there was only one death from carcinoma and local excision is clearly a valid therapy, a conclusion reached by Biggers *et al.*[6]. Early reoperation may occasionally be indicated in suspicious clinical circumstances and careful follow-up remains mandatory.

Over half of the tumours in the present series were of average grade (81 of 152; 53 per cent). There was clearly considerable clinical disquiet about the completeness of excision because 17 of the 81 patients (21 per cent) underwent early reoperation. These doubts appeared largely unfounded as 15 of the 17 patients had no residual disease in the specimen. Despite this cautious approach, 12 of 64 (19 per cent) of the remaining patients developed recurrent disease, in ten of these within tissue that would have been removed at a major excision. Six of these ten patients died as a result of this recurrence, four from carcinoma and two after operation. It was unclear which patients required early reoperation and which could safely be left under careful follow-up. This calls into question the safety of the original procedure.

High-grade tumours were found in 15 (10 per cent) of the 152 patients; conclusions based on such small numbers may not be valid. The original guidelines of Lockhart-Mummery and Dukes[1] that all patients with such tumours should undergo early reoperation was adhered to in six cases. Nevertheless, none of these had residual local growth, although four patients had nodal deposits and two of these died from carcinoma. One patient with no disease in the second specimen died from carcinoma and must be presumed to have had distant spread initially. Despite the diagnosis of a high-grade tumour, early reoperation was not undertaken in nine patients. Only four of these developed recurrent disease, one of whom survived more than 5 years. Thus, overall three of six patients undergoing early reoperation died from carcinoma whereas there were three deaths among nine patients who had no early reoperation. This finding casts doubt on the original tenet relating to high-grade tumours. In certain clinical situations the calculated risk of curative local excision alone for high-grade tumours might be acceptable.

This study suggests that radical local excision alone, provided that the surgeon and pathologist are satisfied about its completeness, is a safe procedure for patients with suitable low-grade tumours. In those with average-grade lesions (overall mortality rate 12 per cent), local excision should not be regarded as acceptable practice. No definite answer can be given on the advisability of immediate major reoperation in patients with high-grade tumours as six of nine such patients without early reoperation survived more than 5 years.

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Multicentre study of a continent colostomy plug

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A multicentre clinical study was carried out to assess the performance of a new disposable device, the Conseal 1-Piece, for colostomy contro and continence. Forty-three patients were studied; none had any complication at the stoma. The time elapsed since surgery and the condition of the stoma and surrounding skin were recorded. The new product was compared with the patients' usual colostomy bag, studying the following parameters: ease of application, reliability, leakage confidence, ease of removal, adhesion and comfort. Thirty-seven patients completed the study. No complications arose, and complete faecal continence was obtained with 71·1 per cent of applications. The plug was kept in position for a mean of 11·5 h and a normal stoma bag was used for the remainder of the day. Of the 37 patients who completed the trial, 26 preferred the Conseal 1-Piece to a colostomy bag. In this preliminary study the device was easy to apply, involved no major complications and provided a high degree of continence. This product deserves further study because of its simplicity of use. However, research to improve the level of continence should continue.

The number of patients with a colostomy in the UK is approximately 100 000 and over 50 000 new end colostomies are created each year in the USA. In Spain it is estimated that 30 000 patients have a colostomy (5000 in Catalonia), of whom more than 1000 have an end colostomy.

Having a stoma can cause considerable physical and psychological problems, sometimes making social reintegration difficult. One reason for this is loss of continence, which may cause the person to feel insecure and dependent. The risk of accidental leakage from the stoma has been reduced in recent years by advances in surgery, the use of mechanical sutures, the dedication and skill of nursing staff and stoma therapists, and improvement in colostomy appliances. All of these measures have helped to improve the quality of life of patients with a stoma. Nevertheless, restoration of continence to a level as near normal as possible must remain the goal. For over 100 years attempts have been made to achieve a continent colostomy by surgical procedures, devices or irrigation, but none has given completely satisfactory results[1].

The present study is an investigation of a new device that promises considerable progress towards the goal of complete continence.

Patients and methods

The study was conducted in seven hospitals. The purpose was to compare the characteristics of the Conseal 1-Piece system (Coloplast, Espergærde, Denmark) with those of an ordinary stoma bag in patients with a colostomy.

This system consists of a plug, similar to a tampon, attached to adhesive material. The plug, which is inserted into the stoma, is made from compressed polyurethane foam covered by a film of polyvinyl alcohol, which reduces by half its original diameter; it is also lubricated with ethylene glycol for easy insertion into the stoma. The polyvinyl alcohol film dissolves quickly (in about 30 s) and allows the foam to expand, the plug thus acquiring a bell-like shape and providing effective sealing that prevents leakage of faeces but allows the passage of gas through an activated carbon filter fitted in it.

Adult patients with a healed left iliac fossa colostomy (diameter 24–45 mm) were included in the study. The stoma showed no evidence of oedema and caused no pain in any of the patients. Some of the patients usually managed the stoma by irrigation.

During the study the patients completed four questionnaires which included: (1) consent to enter into the study; (2) evaluation of the appliance being used before the study; (3) assessment of the number of hours that the plug was kept in place and why it was removed; and (4) evaluation of the plug, using the same parameters as for the usua appliance – ease of application, reliability, leakage, confidence, ease o removal, adhesion and comfort. Each parameter was scored on a scale of 1–5, with 5 representing the best for the patient. All patients included in the study gave fully informed consent before the trial began. The clinical research committees of the hospitals involved also approved the study.

The study group consisted of 43 patients (20 men, 23 women; mean age 58·4 years). The reasons for creation of the colostomy were cance ($n = 40$) and colonic inflammatory disease ($n = 3$). The mean time since surgery was 36·3 (range 1–182) months. The mean diameter o the colostomy was 29·4 (range 25–45) mm. During the study, 14-day training tables were used, which varied according to whether the patients used irrigation or not.

The stomas were assessed as retracted in four patients, flush in 34 and protruding for 2 cm in five. Seven patients had a peristomal hernia and six skin erythema. Nineteen of the 43 patients used irrigation.

Thirty-seven patients completed the study; six withdrew. The participants were classified into two groups according to the use of irrigation.

Results

Table 1 shows the general features of patients included in the study. There were no differences with regard to age, sex ratio, reason for colostomy and stoma characteristics. Assessment of each patient's usual stoma appliance is shown in *Figure 1*.

Six patients withdrew from the study because of leakage of faeces, dislodgement of the plug, pain and lack of confidence. One reported a feeling of fullness, another constant dislodging of the plug, and the final patient was lost to follow-up. One of these patients used irrigation and five did not. In all, 37 patients completed the study.

No complications associated with use of the device were reported by any of the patients who completed the study, except for skin erythema in nine. Patient assessment of the Conseal 1-Piece plug is summarized in *Figure 2*.

A total of 599 plugs were used in the study with a mean of 16 (range 10–20) per patient. Total faecal continence was obtained in 426 applications (71·1 per cent). A feeling of fullness or discomfort was reported with 76 plugs (12·7 per cent) and faecal leakage with 48 (8·0 per cent). In 30 cases (5·0 per cent) there was spontaneous discharge of faeces. In 19 cases other reasons were given to account for removal of the plug.

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able 1 *Details of the 43 patients*

	Irrigation	No irrigation
o. of patients		
Completed	18	19
Withdrew	1	5
Total	19	24
ean age (years)	55·2	60·5
:x ratio (M:F)	10:9	11:13
eason for colostomy		
Cancer	18	22
Other	1	2
ean duration of stoma (months)	44	31
ean stoma diameter (mm)	27·7	30·3
ondition of stoma		
Flush	14	20
Recessed	3	1
Protruding	2	3
eristomal hernia		
Present	1	6
Absent	18	18
:in around stoma		
Normal	18	19
Erythematous	1	5
ıze of plug (mm)		
35	14	14
45	5	10

The plugs were kept in position for a mean of 11·5 h (range 2–24) h, longer in the 18 patients who used irrigation than in those who did not (mean (range) 16·0 (6–24) *versus* 7·1 (2–16) h).

Of the 37 patients who completed the study, 26 preferred the Conseal 1-Piece to their usual stoma bag; 30 per cent preferred the stoma bag.

Discussion

The aim for patients with a colostomy is to regain continence. This is, of course, difficult and, in spite of the use of a variety of procedures, no clear solution has been found for this problem.

In 1982 Schmidt[2] described the creation of an independent or pedicled transplant of autologous muscle around the colostomy, to be performed at the time of colostomy formation or subsequently. Although Schmidt obtained good results (80 per cent continence), others have not had the same success. A Kock reservoir[3], similar to the one used for ileostomy, has also been used, but not very widely because of technical problems and the need for repeated surgery. Another method is the use of upper exteriorization of the colostomy proposed by Ceulemans and Van Baden[4] at the left subcostal level, intended to create a colonic reservoir; this has a low risk of prolapse and is easy to take care of in obese patients. Finally, biofeedback is being assessed for achieving continence[5], but the

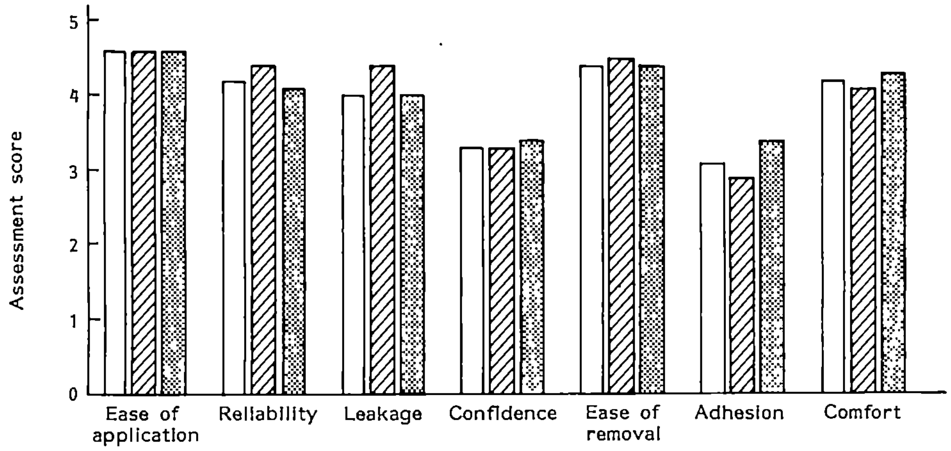

Figure 1 *Assessment of stoma appliances used before the study on a scale of 1–5.* □, *All patients* (n = *43*); ■, *with irrigation* (n = *19*); ▨, *no irrigation* (n = *24*)

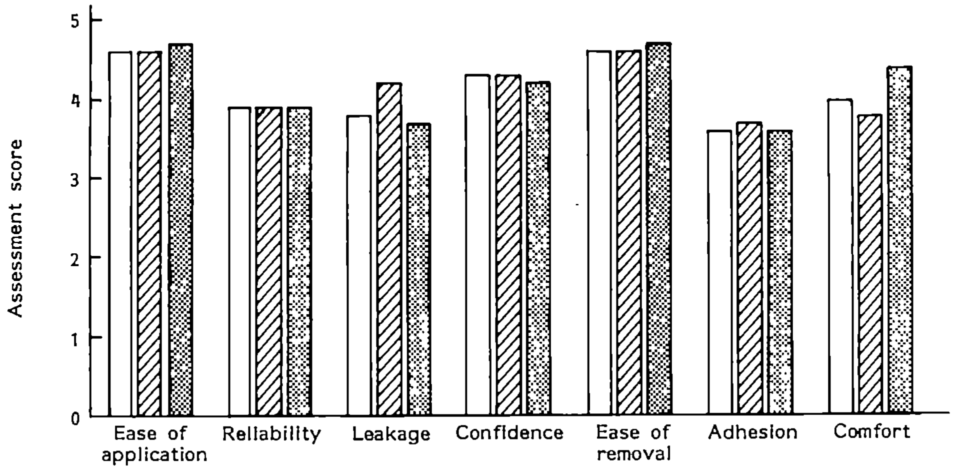

Figure 2 *Assessment of the Conseal 1-Piece system on a scale of 1–5.* □, *All patients* (n = *37*); ■, *with irrigation* (n = *18*); ▨, *no irrigation* (n = *19*)

results are as yet inconclusive. An alternative technique is to train the patient to irrigate the colon, which allows predictable bowel action and reduces the risk of leakage from a full bag.

Research continues into the development of suitable devices for patients with a stoma, to improve the quality of life. Devices have included rubber balloons, the magnetic colostomy[6,7] and a cardboard tube. A few years ago a disposable two-piece plug was produced, which provided continence to some patients with a colostomy. The first results[8] described a continence rate of 86 per cent. Clague and Heald[9], in a series of 46 patients, concluded that the system establishes continence and improves the quality of life in more than one-third of patients with a colostomy.

Recently, a new one-piece plug became available and this led to the present study. The number of patients was low, but as the mean time from surgery was 36·3 months they had a good knowledge of how to handle the colostomy. These patients were therefore demanding with regard to the quality of the product being tested. Six withdrew from the study reporting leakage of faeces, dislodgement of the plug, pain or lack of confidence.

There were no complications reported from the 37 patients who completed the study, except skin erythema in 24 per cent; this problem already existed in 14 per cent of the 43 patients who joined the study.

Another study[10], of similar duration (15–20 days), patient characteristics (age, sex and features of the stoma) and rate of plug usage, reported that 80 per cent of patients considered the plug useful. Some 37 per cent preferred it to the stoma bag; 33 per cent declared that it provided a better quality of life; and 39 per cent found disadvantages to its use[10].

Irrigation may have a significant effect on stoma management. There has been a report[11] of 24-h continence in 86 per cent of patients, while 5 per cent have perfect control over 48 h. Other authors[12] have described 97 per cent of patients obtaining continence for 24 h, with 42 per cent still using irrigation. However, in a series from the Mayo Clinic[13], only 69 per cent of patients obtained continence by irrigation and 18 per cent withdrew from the study.

The present study was based on two groups of patients: those who used irrigation ($n = 19$) and those who did not ($n = 24$). The results were similar in both groups (*Figures 1* and *2*), except that only one patient withdrew in the first group while there were five in the second. Patients in both groups stressed confidence and easy handling of the product, and gave high scores for ease of insertion and removal. For most patients use of the product solved the embarrassment of noises produced by gas, as well as smell, a problem that still exists when patients practise irrigation alone.

In patients using irrigation the plug was left in position for longer, the safety provided was greater (16·0 *versus* 7·1 h) and fewer plugs were needed (one *versus* two or three a day). Reliability was increased in both groups during working hours and social activity.

In conclusion, the Conseal 1-Piece system has a place in th care of patients with a stoma as it is easy to apply, requires n surgical insertion and causes no major problems. Complet continence is provided in a large proportion of patients, wheth or not they employ irrigation. A continued effort should b made to find the ideal system for use in all patients. In th meantime, it would be of interest to conduct a study in th immediate postoperative period with large numbers of patients

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Anorectal function after preoperative intraluminal brachytherapy and colonic J pouch–anal anastomosis for rectal carcinoma

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The effects of preoperative intraluminal brachytherapy on bowel function after anoabdominal rectal resection and colonic J pouch–anal anastomosis were studied. The patients included eight not receiving irradiation (group 1), eight who received 30 Gy (group 2) and eight who received 80 Gy (group 3). Stool frequency and the incidence of soiling were significantly greater in group 3 than in the other groups. Anal resting pressure was lower in group 3 during the study period but J pouch distensibility was not reduced. The maximum tolerated volume, threshold volume and squeeze pressure were significantly lower in group 3 than in the other groups in the early postoperative period. These results suggest that high-dose brachytherapy affects the anal sphincters and colonic J pouch. A moderate dose of 30 Gy may be more suitable before restorative anorectal surgery.

urgery for rectal carcinoma includes rectal excision with a ermanent stoma and sphincter-preserving procedures. A ecent choice has been operations attaining restoration of ntestinal continuity, for which similar oncological results have een reported[1,2]. Such procedures have two problems: how to pproach the tumour located deep in the pelvis and how to econstruct the neorectum in continuity with the anus. A variety f combined procedures, such as abdominal pull-through urgery[1,3–7], transanal techniques[8] and a trans-sphincteric peration[9], have been described. The introduction of circular taplers has made it easier to restore intestinal continuity, specially in patients with tumours of the lower two-thirds of he rectum. Efforts to prevent recurrence in this setting include djuvant radiotherapy[10] and/or systemic chemotherapy.

Remote afterloading intraluminal brachytherapy has been sed before operation since 1986 in this department. The aims f preoperative intraluminal brachytherapy are to improve urvival by increasing tumour resectability and to reduce the ncidence of patients requiring a permanent stoma. This study nvestigated the functional results after intraluminal brachyherapy and sphincter-saving surgery.

atients and methods

atients

ixty patients underwent anoabdominal rectal resection and colonic J ouch–anal anastomosis between May 1986 and December 1991. orty-five patients received preoperative intraluminal brachytherapy 2 eeks before surgery. Preoperative brachytherapy was given in a andomized trial until June 1989. Patients without postoperative omplications and/or local recurrence were selected for studies of norectal function during the follow-up period (15 months after urgery). Patients were designated: group 1, receiving no irradiation, roup 2, receiving moderate-dose brachytherapy (30 Gy) and group , receiving high-dose brachytherapy (80 Gy). Each group contained ight age-matched patients; there were no significant differences etween groups for tumour characteristics. Details of the patients are hown in *Table 1*. Informed consent was obtained in all cases.

adiotherapy

atients were treated with a remote afterloader RAL-30A (Toshiba, okyo, Japan) and a tandem applicator. The irradiation source was obalt-60 with an activity of 1·7 or 2·6 Ci (63 or 96 GBq). Before rradiation, the proximal and distal borders of the tumour were detected by colonoscopy and marked on the skin under fluoroscopic guidance. To maintain the patient in the correct position during irradiation and to fix the tube that was inserted and connected to the machine as a pathway for the cobalt-60 source, a tailor-made shell was prepared for each patient. The patient was treated in the left lateral position. Doses at a point 5 mm below the mucosa were calculated using a computer.

Table 1 *Clinical details of the three groups of patients studied*

	Group 1	Group 2	Group 3
No. of patients	8	8	8
Intraluminal brachytherapy dose (Gy)	0	30	80
Median (range) age (years)	59 (38–72)	58 (34–76)	61 (38–78)
Sex ratio (M:F)	5:3	6:2	5:3
Tumour characteristics			
Histological grade			
Low	6	6	7
Middle	2	2	1
High	0	0	0
Median (range) distance from anal verge (cm)	5·3 (3·5–8·5)	5·3 (3·0–8·0)	5·3 (2·5–8·0)

Surgical technique

The technique has been described previously[11].

Manovolumetry

Manovolumetric assessment was performed before brachytherapy, 2 weeks after irradiation, before closure of the stoma, and from 1 month to 1 year after stoma closure. The methods of measuring anal canal pressure, rectoanal inhibitory reflex, pouch volume and compliance have been described previously[11,12].

Statistical analysis

Comparisons were performed with the Mann–Whitney U test including a Bonferroni adjustment; $P < 0·05$ was taken to be significant.

Results

Bowel function

Changes in daily stool frequency are shown in *Figure 1a*. There were no significant differences in stool frequency between

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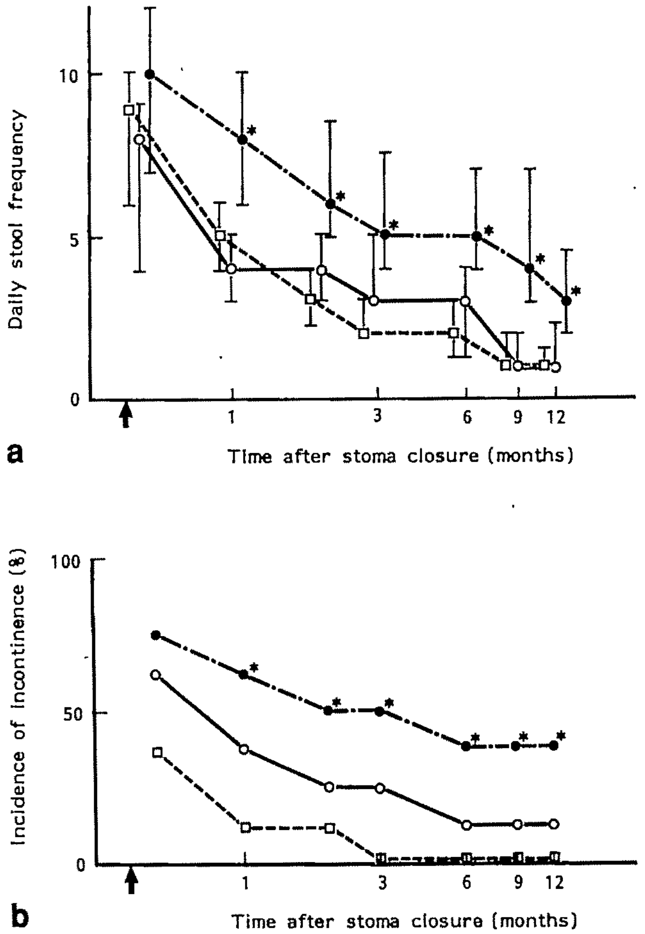


Figure 1 a *Median (interquartile range) daily stool frequency and* b *incidence of incontinence after coloanal anastomosis and stoma closure* (⬆). □, *Group 1;* ○, *group 2;* ●, *group 3.* *P < *0·05* versus *group 1* (*Mann–Whitney* U *test*)

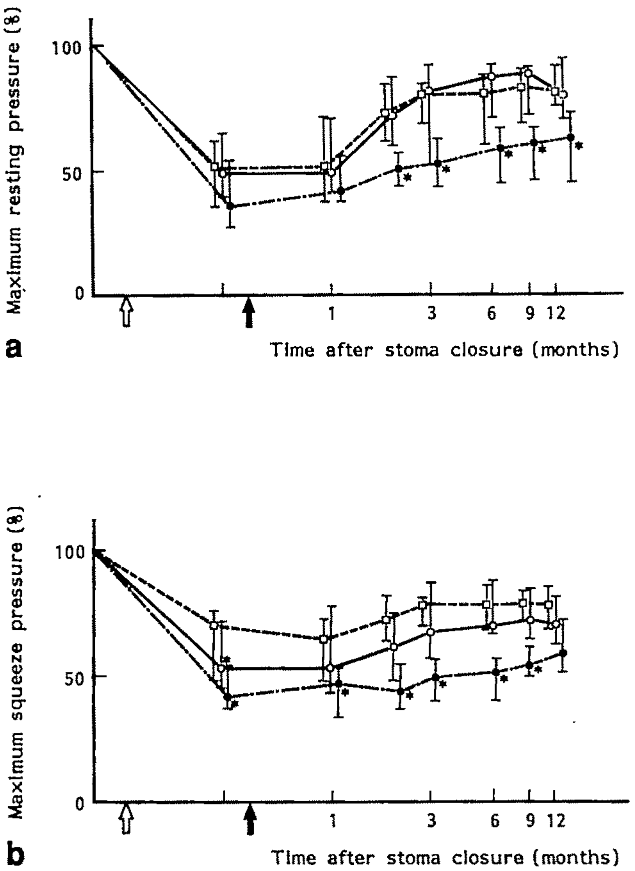


Figure 2 *Recovery of median (interquartile range)* a *maximum restin pressure and* b *maximum squeeze pressure relative to preoperative valu after coloanal anastomosis* (⇧) *and stoma closure* (⬆). □, *Group 1;* ○ *group 2;* ●, *group 3.* *P < *0·05* versus *group 1* (*Mann–Whitney* U *test*)

groups 1 and 2. Patients in group 3 had a higher frequency throughout the observation period. *Figure 1b* shows the incidence of incontinence, which was markedly reduced in the first 6 months in groups 1 and 2. Urinary incontinence was observed in no patient. One patient in group 1, two in group 2 and four in group 3 needed medication (mainly laxatives) to modify bowel function after stoma closure.

Manovolumetry

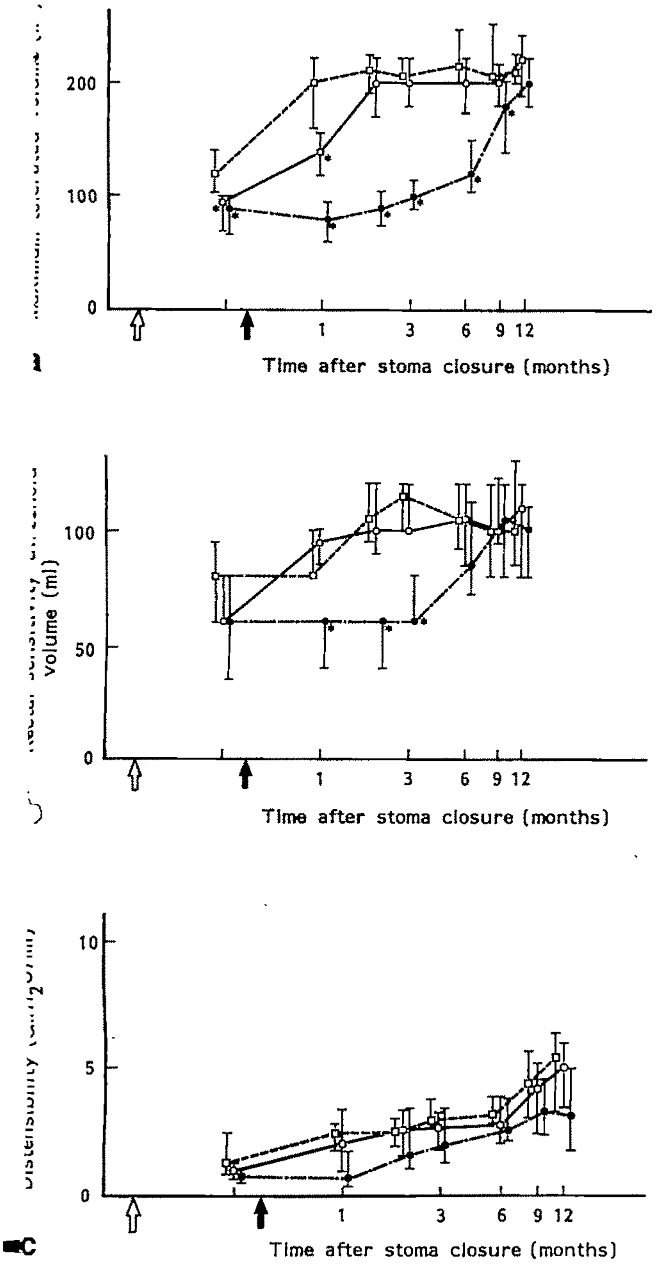
Patients in group 3 had lower resting and squeeze pressures, a higher frequency of slow waves, a higher incidence of an absent inhibitory reflex and a lower maximum tolerated volume than those in the other two groups. A time-course analysis of anal canal and colonic J pouch function was carried out (*Figures 2* and *3*). Preoperative median (interquartile range) values of resting anal pressure were: group 1, 80·0 (60·0–83·7) cmH_2O; group 2, 92·6 (69·8–100·5) cmH_2O; and group 3, 71·4 (55·8–96·3) cmH_2O. The percentage recovery in maximum resting pressure was no different in groups 1 and 2 at any time during the study period, but patients in group 3 consistently showed lower pressures. Maximum squeeze pressure showed a similar profile to resting pressure but a marked recovery in group 3 was observed over 6 months after stoma closure. These data suggest that damage to the internal anal sphincter was more severe and persistent than that to the external sphincter in this group. Although distensibility was not reduced, the maximum tolerated volume and threshold volume of the J pouch were lower within the first 6 months in group 3. Both these volumes recovered to the levels in the other two groups 1 year after stoma closure.

Discussion

In this series, tumours located 2·5–8·5 cm from the anal verg were treated by anoabdominal rectal resection and colonic pouch–anal anastomosis. Intraluminal brachytherapy wa applied before surgery to decrease the tumour mass a operation. A pilot study indicated a lower local recurrence rat after brachytherapy compared with non-irradiation but it i also important to achieve a good functional result after surgery Irradiation could affect structures that are related to anorecta function such as the internal and external anal sphincters, th anal verge, and the distal sigmoid colon and/or J pouch.

Anal canal pressure in group 1 recovered to 80 per cent o the preoperative value 1 year after stoma closure. Decrease tone may result from anal dilatation and/or transection at th rectoanal junction removing the intrinsic nervous pathway controlling the internal sphincter. Patients who received 80 G of brachytherapy had a lower resting pressure and lower squeeze pressure than those not receiving irradiation or those given 30 Gy of brachytherapy. Squeeze pressure and resting pressure did not recover even 12 months after stoma closure. Patients given moderate-dose brachytherapy had the same level of ana canal function as those without irradiation.

The marked damage to the myenteric plexus of the distal colon and rectum seen histologically after radiotherapy[13] may be responsible for the poor pouch function indicated by the absence or reduction in amplitude of the rectal distension reflex in the present patients. The hypertrophy of smooth muscle seen on histological examination may be further evidence of damage to the myenteric plexus, as there is some evidence that denervated smooth muscle undergoes hypertrophy[14].



lgure 3 *J pouch function characterized by median (interquartile range) maximum tolerated volume,* **b** *rectal sensitivity threshold volume and distensibility after coloanal anastomosis* (⇧) *and stoma closure* (⬆).], *Group 1;* o, *group 2;* ●, *group 3.* *$P < 0{\cdot}05$ versus *group 1 Mann–Whitney* U *test)*

The manovolumetric findings suggest that radiation damage o the internal anal sphincter and colonic J pouch are important actors in the poor early postoperative results. Delayed adiation injury appears after an interval of 6 months to 30 years and results from progressive ischaemia[15]. By contrast, early radiation damage occurs during treatment and is caused by reversible direct injury to the rectal mucosa and anal verge[16]. Perianal skin ulcers and infection resulted in poor postoperative function in some of the present patients in group 3. Moderate-dose brachytherapy did not have such adverse effects and good bowel function was achieved, as was the case in patients not receiving brachytherapy. Three patients in group 3 underwent abdominoperineal excision due to dosage irradiation. This suggested that the dose was too high or the field too wide.

In conclusion, the present data suggest that moderate-dose intraluminal brachytherapy of 30 Gy and anoabdominal rectal resection with colonic J pouch–anal anastomosis provides a good treatment for low rectal cancer.

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Pouch–vaginal fistula

Between January 1976 and June 1991, 161 women underwent restorati proctocolectomy. Seventeen (10·6 per cent) developed pouch–vagin fistula. There was no difference in the incidence of inflammatory (15 141; 10·6 per cent) and non-inflammatory (two of 20; 10 per cen disease, the severity of colitis or the number of stages in the operatio In 15 patients the fistula involved the ileoanal anastomosis; in two had possibly occurred at the dentate line. There was no significa difference in the proportion of hand-sewn (ten of 120; 8·3 per cent) ar stapled (seven of 41; 17 per cent) ileoanal anastomosis. Of the women, six had pelvic sepsis in the immediate postoperative period ar five had an anastomotic complication. There was no case of Crohn disease. Three patients developed a pouch–vaginal fistula before closu of the ileostomy. The remaining 14 fistulas occurred a median of (range 1–144) months after closure. Five further patients were referre from elsewhere to give a total of 22 for analysis of treatment an outcome. The fistula developed before ileostomy closure in five patien (group 1) and after closure in 17 (group 2). Following treatment, s fistulas had healed with five patients still undergoing treatment. In grou 1, three of the five fistulas healed, whereas in group 2 only three of th 17 healed. Eight patients required excision of the pouch. The prognos appears to be worse when pouch–vaginal fistula occurs after ileostom closure. The optimal management is not yet established.

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Fistulation from the ileal reservoir into the vagina after restorative proctocolectomy is an uncommon but serious complication. It represents an important cause of failure of the operation, largely because it is difficult to treat. Pouch–vaginal fistula was first reported 7 years after Parks' description of the operation[1,2]. Subsequently the reported incidence has ranged from 6·9 to 17 per cent[3,4]. Although there is some information on fistula from the ileal reservoir to various sites[5], there is little in the literature specifically dealing with pouch–vaginal fistula. The authors therefore reviewed experience of this complication with reference to aetiological factors, management and outcome.

Patients and methods

Between January 1976 and June 1991, a total of 355 patients underwent restorative proctocolectomy. They included 161 women, of whom 17 (10·6 per cent) developed pouch–vaginal fistula. Possible predisposing factors (*Table 1*) were determined from examination of case notes. The timing of occurrence and site of the fistula were noted. The surgical technique as originally described[1] had changed over the years. Four different types of ileal reservoir had been used according to the preference of each surgeon. These included the three-loop (S pouch) (20 patients), two-loop (J) (33), four-loop (W) (83) and ileoanal Kock (25). The ileoanal anastomosis was hand-sewn in 120 patients and stapled in 41. In the latter group, 26 were single (purse string) and 15 double stapled. A loop ileostomy was established in 149 patients for a minimum of 2 months and closed only when the pouch and ileoanal anastomosis were clinically and radiologically intact. In 12 women no ileostomy was fashioned. All patients received perioperative antibiotics and drainage of the pelvis.

A further five women referred for management of pouch–vaginal fistula were included in the analysis of treatment and outcome.

The outcome of fistula surgery was defined as successful if the fistula remained healed at least 6 months after closure of the ileostomy. Surgery was unsuccessful if the fistula remained unhealed or recurred after operation. The outcome was pending (or awaited) if the patient was within 6 months of having either fistula surgery with no ileostomy or closure of the covering ileostomy.

The χ^2 test with Yates' correction was used for statistical analysis.

Table 1 *Clinical details recorded from case notes*

- Preoperative factors
  - Presenting disease
  - Previous colectomy
  - Experience of surgeon
- Intraoperative factors
  - Pouch type
  - Rectal cuff length
  - Anastomotic technique
  - Mucosectomy
- Postoperative factors
  - Complications
    - General
    - Specific: pelvic sepsis, ileoanal anastomotic dehiscence
- Outcome

Results

Site and timing of fistulation

The internal fistula opening was situated at the ileoana anastomotic suture line in 15 patients and appeared to lie a the dentate line in two. The vaginal opening was in the lov vagina or labial region in 16 women, in two of whom then was extension into the proximal vagina. In a further case th vaginal opening was high up on the posterior wall approachin the fornix.

The incidence over the study period is shown in *Figure 1* In the first 6 years there was only one case in 20 patients although a further patient in this group developed a fistula afte 12 years. During the next 8·5 years there were 16 cases occurring at a rate of nearly two per year.

In three patients the fistula developed before closure of the ileostomy within the immediate period after restorative proctocolectomy. In 14 it developed a median of 7 (range 1–144) months after ileostomy closure (one patient who had no ileostomy is included).

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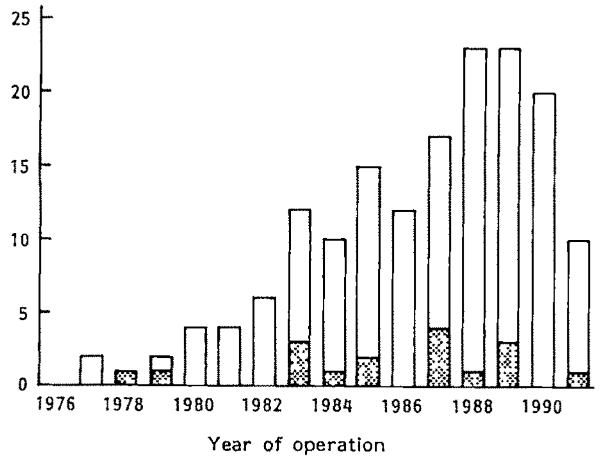


ure 1 *Incidence of pouch–vaginal fistula (▨) in 161 women after torative proctocolectomy*

ble 2 *Clinical and surgical details in 161 women who underwent torative proctocolectomy*

	No.	Pouch–vaginal fistula
ease		
lcerative colitis	141	15 (10·6)
FAP	17	1 (6)
Other	3	1 (33)
vious colectomy for erative colitis		
Yes	69	10 (14)*
No	72	5 (7)
uch design		
S	20	2 (10)
J	33	9 (27)†
W	83	5 (6)
Kock	25	1 (4)
oanal anastomosis		
Hand-sewn	120	10 (8·3)
Stapled		
Single	26	4 (15)
Double	15	3 (20)
Total	41	7 (17)‡

lues in parentheses are percentages. FAP, familial adenomatous lyposis. *$P = 0.30$; †$P = 0.03$; ‡$P = 0.27$ (χ^2 test)

esenting disease

here was no relationship between the presenting disease and cidence of pouch–vaginal fistula (*Table 2*). No patient with cerative colitis was subsequently considered to have Crohn's sease. Two women had a rectovaginal fistula at the time of storative proctocolectomy. There was no difference between tients who had undergone initial colectomy before the oanal procedure and those who had not.

rgical technique

here was a significantly higher incidence of pouch–vaginal stula in patients having a two-loop (J) reservoir compared ith the other designs (*Table 2*).

Until 1981 the length of retained rectal cuff denuded of ucosa was 6–8 cm. Thereafter the entire rectum was removed, aving only an anal stump. When a hand-sewn ileoanal nastomosis was used, mucosectomy of this was carried out. patients having stapled anastomosis, no mucosectomy was erformed. In general, three-loop (S) reservoirs had a long ctal cuff whereas all other designs did not. Ten (8·3 per cent) 120 patients who had mucosectomy and hand-sewn nastomosis and seven (17 per cent) of 41 who had no ucosectomy and a stapled anastomosis developed pouch–vaginal fistula. There was no significant difference between these groups.

Postoperative complications

Pelvic sepsis occurred in six patients and an ileoanal anastomotic complication such as defect or stricture requiring dilatation was seen in five (*Table 3*). Both these rates were significantly higher than in patients who did not develop pouch–vaginal fistula (*Table 3*). In six patients there was no associated septic or anastomotic complication. There was no relationship between the incidence of pouch–vaginal fistula and general complications including enterocutaneous fistula (two patients) and wound infection (two), but other perianal fistulation was present in five women.

Treatment

In reporting the results of treatment, the five cases referred from elsewhere are considered with the authors' own 17 patients. Two of the five had had a pelvic abscess, in two no obvious predisposing cause was evident and one was subsequently diagnosed as having Crohn's disease (the only such case in the whole series).

The 22 patients were divided into group 1 (five patients), in whom the fistula appeared before closure of the ileostomy, and group 2 (17) in whom it appeared after.

Group 1. The fistula initially healed without operation in three patients (*Figure 2*). Treatment included antibiotics and in one case drainage of the pouch by an indwelling balloon catheter for 9 days. In two of these three patients, however, the fistula recurred after closure of the ileostomy at 1 week and 3 months. In one of these the fistula was almost asymptomatic and closed spontaneously after 2 years. In the other, a further ileostomy was necessary and the fistula remains unhealed.

Table 3 *Postoperative pelvic sepsis and ileoanal anastomotic complications in 161 women*

	No pouch–vaginal fistula ($n = 144$)	Pouch–vaginal fistula ($n = 17$)
Pelvic sepsis	17 (11·8)	6 (35)*
Ileoanal anastomotic complications only	6 (4·2)	5 (29)†
No complication	121 (84·0)	6 (35)‡

Values in parentheses are percentages. *$P = 0.07$; †$P = 0.004$; ‡$P = 0.1$ (χ^2 test)

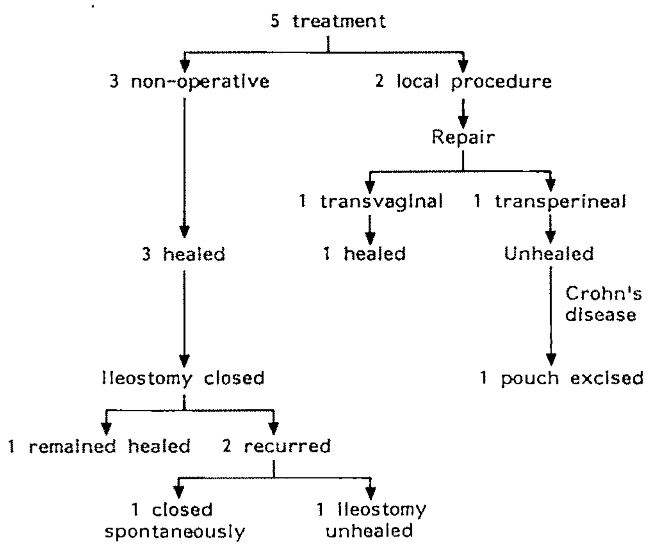


Figure 2 *Outcome of pouch–vaginal fistula developing before ileostomy closure (group 1)*

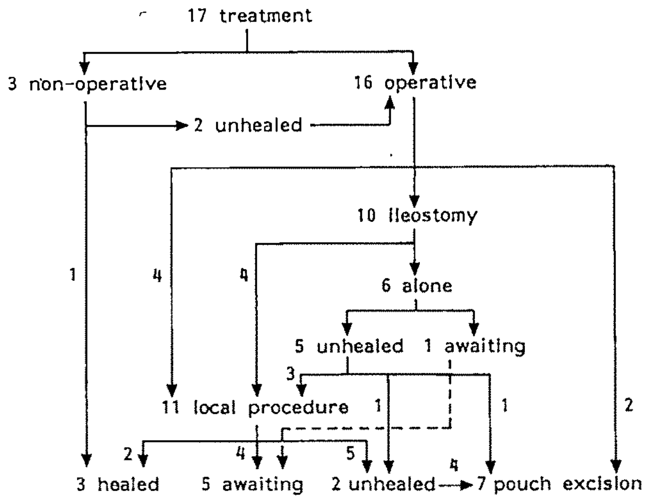


Figure 3 *Outcome of pouch–vaginal fistula developing after ileostomy closure (group 2)*

Table 4 *Local procedures for pouch–vaginal fistula carried out in 13 patients*

	No.	Success	Failure	Result uncertain
Fistulotomy	4	1	1	2
Fistulectomy and sphincter repair	1	0	1	0
Direct repair				
Perineal	6	1	4	1
Vaginal	1	1	0	0
Advancement flap	2	0	1	1
Resuture of ileoanal anastomosis	2	0	2	0

Fistulas in two patients were treated operatively by direct repair. In one a transvaginal approach was used successfully. In the other a transperineal approach was adopted but failed. However, Crohn's disease was subsequently diagnosed and the pouch excised. The outcome at the time of review in the five patients in group 1 was closure in three, unhealed in one and excision of the pouch in one.

Group 2. Of the 17 patients, three were initially treated without operation; one fistula closed spontaneously at 18 months and two women underwent surgery, at 5 and 12 months. The initial operative treatments adopted can be divided into four groups: local surgery alone (four patients), ileostomy alone (six), ileostomy with local procedure (four) and excision of the reservoir (two) (*Figure 3*).

Of the four patients treated by local surgery alone, in one the fistula healed after fistulotomy at 14 months and two required further local surgery with ileostomy; in one the fistula healed and in the other the outcome is uncertain. One patient who developed pouch–vaginal fistula 4 months after caesarian section underwent fistulotomy and insertion of a seton suture. The outcome is awaited.

Of the six patients initially treated by ileostomy alone, the fistula failed to close in five and outcome is awaited in one. Four of these had further surgery after a median interval from re-establishment of the ileostomy of 6 (range 4–10) months. One patient with persistent perianal fistulation underwent excision of the pouch. Two had multiple local procedures in an attempt to close the fistula but in both these failed and the pouch was excised. In one patient the ileoanal reservoir was converted into an abdominal Kock pouch, although subsequent enterocutaneous fistulation necessitated pouch excision. In one the fistula remained unhealed at 22 months without furt treatment.

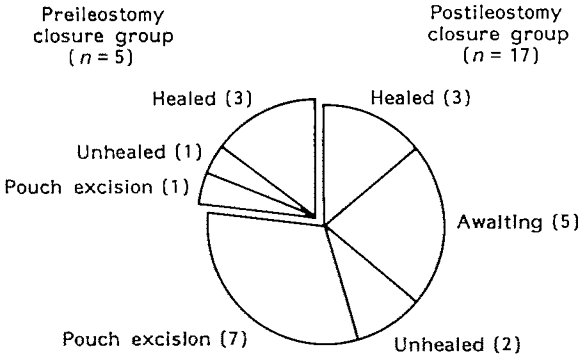


Figure 4 *Final outcome of pouch–vaginal fistula*

One of the four patients treated by ileostomy with simultaneous local procedure had an unhealed fistula at months, outcome in two is awaited and in the other the reserv was excised following retraction of the pouch after an attem to resuture the ileoanal anastomosis.

Two patients had the reservoir excised as the init treatment; one had a large fistula extending into the posteri fornix and poor sphincter function. The other presented wi severe pelvic sepsis and perineal fistulation clinically suggesti of Crohn's disease, although this was not subsequen confirmed histologically. Of the 17 patients in group 2, t outcome at the time of review was closure in three, persisten in two, uncertain in five and pouch excision in seven.

Local procedures

Patients in both group 1 (two) and group 2 (11) underwent total of 16 local procedures (*Table 4*). Three fistulas we treated successfully, giving a success rate for local procedur of 19 per cent. The outcome is presently uncertain in a furth four patients.

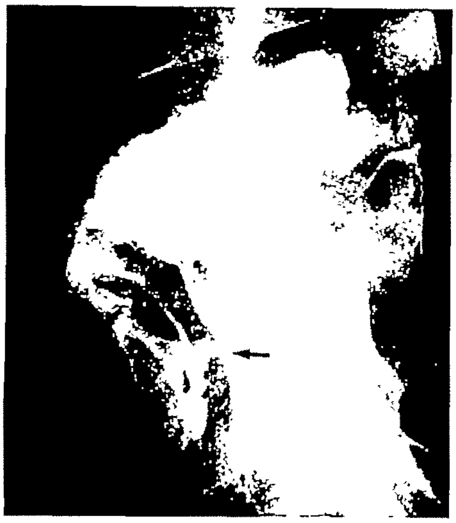
Outcome

Overall, six of the 22 fistulas had healed with five patients st awaiting a definite outcome. *Figure 4* shows that in group the fistula healed in three of five patients, whereas in group only three of 17 healed. Eight patients required excision of t pouch; all had a patent fistula at the time. Crohn's disease w confirmed in one patient on examination of the excised pouc In a further patient this disease was suspected because perineal fistulation but was not confirmed on histologic examination after pouch excision.

Discussion

Pouch–vaginal fistula was first reported by Wong *et al* in 1985 and subsequent rates have varied from 4 t 16·7 per cent[5–8]. In 1989, Wexner *et al.*[3] reported 21 cases, a incidence of 6·9 per cent, from a survey of colorectal units i North America. More recently, Keighley *et al.*[4] reported eig pouch–vaginal fistulas among 114 female and male patien (presumably with a denominator in the former of about ha this number) and N. J. McC. Mortensen *et al.* (person communication) experienced six fistulas in their first 36 femal patients.

In the present series, pouch–vaginal fistula was rare in th early years: two occurred in the first 6 years to 1982, giving a incidence of 5 per cent. Subsequently there have been 16 fistula in 142 female patients operated on, giving an incidence sinc 1983 (inclusive) of 11 per cent. This suggests that the incidenc of pouch–vaginal fistula has increased with time. One reaso for this is likely to be the length of follow-up, as discusse above. However, there may also be other factors and it i possible that surgical experience or differences in technique pla a part. The present results suggest that experience is not



;ure 5 *Pouchogram showing a pouch–vaginal fistula; the fistula row) overlies the vagina. Contrast was injected through an anal heter*

:tor. The complication was rare in the first 6 years, but has come more common since. Three principal changes in :hnique have taken place over the past 10 years since the croduction of restorative proctocolectomy. These include the ıgth of the retained rectal cuff, the type of pouch and the :hnique of ileoanal anastomosis. In the early years the rectal ff was left long to measure 6–8 cm from the anal verge so as minimize the possibility of incontinence. The long rectal cuff s soon recognized to be a source of morbidity and a ntributing factor to failed spontaneous evacuation. The cuff ıs thus shortened, which made mucosectomy much easier and ıabled the newer designs of reservoir to be joined directly to e anal canal. Although this improved function and allowed liable spontaneous defaecation, it may have exposed the tient to a greater risk of pouch–vaginal fistula. It could well : that a long rectal cuff provided protection to the vaginal ıll. In *Figure 5* the close proximity of the vagina to the ileoanal ıastomosis is clearly seen.

The three-loop (S) reservoir caused a high incidence of acuation difficulties because of the long efferent limb. As a sult it was replaced by the two- (J) and four- (W) loop ›uches, which improved defaecation with no compromise of ›ntinence[9]. From the results of the present series it might seem at pouch–vaginal fistula is related to the type of reservoir. he incidence associated with the two-loop (J) pouch was per cent compared with 10 per cent for the three-loop (S) ›uch. However, fistulation occurred in only 6 per cent of ıtients having a four-loop (W) reservoir, suggesting that the ›sence of an efferent limb *per se* is not a factor contributing pouch–vaginal fistula. The higher incidence after J construction could be a reflection of the associated use of a apled ileoanal anastomosis (see below). Pouch–vaginal stula following a Kock ileoanal reservoir, however, was ıcommon (4 per cent) and yet 21 of the 25 patients had a apled anastomosis.

The incidence of pouch–vaginal fistula after stapled ıastomosis was twice that seen after suture, although the ifference was not significant. With the hand-sutured technique e pouch is brought to the dentate line after mucosectomy of e retained anal stump. It is possible that sutures placed in e anterior part of the anastomosis might incorporate the ıginal wall, thus promoting a potential fistula. With stapled ıastomosis, the gut tube is divided at the anorectal junction ithout mucosectomy. Whether the single- or double-staple :chnique is used, the anastomosis lies in direct apposition to e posterior vaginal wall without any intervening rectovaginal :ptum. It is possible to incorporate the vaginal wall into the aple line, but care was taken to ensure that this did not happen and there was no evidence in any case of it having occurred. What effect staples have in this region is unknown. They can produce a local fibrous reaction and may possibly have a direct mechanical effect on tissue with which they are in contact. In the case of the double-staple technique, perhaps minor sepsis can occur at the lateral limits of the transverse staple line. In one patient the stapling instrument did not close properly. Longer follow-up in more patients is required to answer the important question of whether stapling increases the risk of this complication.

Pouch–vaginal fistula was not disease related in the present study as others have suggested[3]. Although the numbers are small, there was no statistical difference between the diagnostic groups. Neither was there any evidence that a three-stage rather than two-stage procedure was more likely to predispose to fistulation. This might suggest that the severity of proctitis is not a factor. Pelvic sepsis is, however, a major determinant. Of the present patients with fistula, 65 per cent had developed pelvic sepsis or anastomotic complication compared with 16 per cent of the 144 women who underwent restorative proctocolectomy during the same period and did not develop a fistula. There was no evidence that stricture of the ileoanal anastomosis was a causative factor.

Of the late fistulas, two appeared to have occurred just distal to the ileoanal anastomosis at the level of the dentate line. If so, this suggests that fistulation may be unrelated to the surgery itself. Ulcerative colitis is associated with a higher incidence of fistula *in ano* and rectovaginal fistula. With the stapled technique of ileoanal anastomosis for restorative proctocolectomy, a rim of anorectal mucosa is left *in situ*. In patients with ulcerative colitis this retained diseased rim of mucosa could predispose to fistula formation. Alternatively, cryptoglandular infection in the anal glands may occur leading to sepsis and fistulation; perhaps the liquid stool from the pouch increases the risk of a fistula arising in previously healthy tissue.

Crohn's disease has been reported to be more common in patients with pouch–vaginal fistula. It was found in 12 per cent of patients with this complication in the North American multicentre study[3] and accounted for 60 per cent of the pouches excised. Keighley *et al.*[4] reported that three of eight patients with pouch–vaginal fistula were thought to have Crohn's disease and Schoetz *et al.*[7] found this condition in one of three patients. In the present series, only one of 22 women had proven Crohn's disease. Although another developed typical signs of perianal Crohn's disease, there was no histological confirmation from the resected specimen after excision of the pouch.

The results of this study suggest that the prognosis may be influenced by the time of development of pouch–vaginal fistula. When the fistula occurred before closure of the ileostomy the chance of fistula closure appeared to be better than when it formed afterwards. In group 1 the fistula tended to be small and two of the five lesions healed without a local procedure. Similar success in this group of patients was reported by others with a 50 per cent rate of ultimate healing[3]. In contrast, if pouch–vaginal fistula occurred after closure of the ileostomy the prognosis was poor. There seems to be little prospect of closure occurring after a simple ileostomy as none of these fistulas healed without further management. In this group, the fistula tends to be larger and sepsis more severe. This probably accounts for the high pouch excision rate of 41 per cent. Others have reported a similar experience after ileostomy alone, with only 13 per cent of fistulas closing with this treatment and an overall successful outcome of 57 per cent[3].

Local procedures have been adapted from those used for the treatment of rectovaginal fistula. The vaginal route was used in only one of the present patients, in whom it was successful. A transperineal approach in which wide dissection of the pouch–vaginal septum was carried out was successful in only one of six cases in which it was employed. The endoanal ileal advancement flap technique[6] initially described by Greenald and Hoexter for rectovaginal fistula was used in two patients. This was unsuccessful in one and the outcome is awaited in the other. This type of repair may be technically difficult after restorative proctocolectomy because of the narrow, sometimes strictured, ileoanal anastomosis. This approach is, however, favoured by Wexner *et al.*[3], who reported success in three of five patients so treated. Fleshman *et al.*[10] used the technique for anastomotic dehiscence (not pouch–vaginal fistula) with successful closure of the defect in six of nine cases. However, late failure can occur and long-term follow-up is essential to define the ultimate success of any local procedure.

In the present series, two patients were treated by detachment of the ileoanal anastomosis and resuture more distally, as has been described in the treatment of rectovaginal fistula with coloanal anastomosis. This failed in both patients owing to proximal retraction of the small bowel reservoir in the postoperative period. Using this procedure, however, Fleshman *et al.*[5] succeeded in three of seven patients with fistula other than of the pouch–vaginal type.

One patient who had undergone an attempt at direct repair and addition of an advancement flap was treated by laying open of the fistula with delayed sphincter repair. After closure of the ileostomy, however, pelvic sepsis recurred and the pouch had to be removed.

Others have reported success in a few patients with the interposition of gracilis or perineal muscle, or vulval fat pads[3,11,12]. There is no experience of these procedures in treating the present patients. If the long-term outcome in larger numbers of patients is successful, it may be that this method will become the procedure of choice.

At present, the following conclusions regarding treatment of pouch–vaginal fistula are justified. Crohn's disease must first be excluded. A fistula occurring before closure of the ileostomy may heal spontaneously; if it does not, a local procedure may lead to closure. If the fistula appears after restoration of bowel continuity, there is a chance of closure if the fistula is small. If not, the pouch should be defunctioned and a local procedure carried out when sepsis has settled. Defunction alone appears unlikely to result in healing. The present study has shown no particular procedure to be preferable and further experience is necessary to define the best surgical approach.

Acknowledgements

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A selection from the June issue of the American journal.

arathyroid hormone secretion after peration for primary yperparathyroidism

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ckground. *Primary hyperparathyroidism (pHPT) is asso- ated with a defective regulation of the secretion of parathyroid rmone (PTH). Thus in pHPT, higher than normal calcium ncentrations are required to inhibit PTH release. However, it not known if this defective regulation is normalized by moval of the parathyroid adenoma (i.e., whether the gulation of PTH secretion is normal in the remaining ands). In this study we therefore investigated the PTH cretion in patients operated on for parathyroid adenoma 1 ar after operation.*

ethods. *Na_2 ethylenediamine tetraacetic acid and $CaCl_2$ ere infused at constant rates in six patients operated on for rathyroid adenoma and six healthy individuals. Serum vels of intact PTH and ionized calcium were determined uring the infusions.*

esults. *No significant differences between the two groups ere found in baseline levels of serum ionized calcium and TH. Furthermore, no significant differences between patients nd control subjects were found in the maximum serum PTH vels during the hypocalcemic infusion of ethylenediamine traacetic acid or in the minimum serum PTH levels during e calcium infusion. In contrast, the set point (the calcium ncentration required for half-maximal inhibition of PTH cretion) was significantly lower in the patients (1.20 ± .01 mmol/L) compared with control subjects (1.22 ± 0.01 mol/L; $p < 0.05$).*

onclusions. *We conclude that the elevation of set point in atients with parathyroid adenoma is corrected by successful peration. This suggests a monoclonal origin of parathyroid denomas. (SURGERY 1993;113:649–54.)*

hear stress modulates the roliferation rate, protein synthesis, nd mitogenic activity of arterial mooth muscle cells

ntonio V. Sterpetti, MD, Alessandra Cucina, PhD,
uciana Santoro D'Angelo, PhD, Barbara Cardillo,
hD *and* **Antonino Cavallaro, MD,** *Rome, Italy*

ackground. *The aim of this study was to determine the orrelation between hemodynamic forces and proliferation of mooth muscle cells (SMC).*

ethods. *Bovine arterial SMC were seeded in a fibronectin- oated polystyrene cylinder at 5×10^5 cells/tube and allowed to each confluence and to adhere for 48 hours. The experimental groups were subjected to a laminar flow of 150 ml/min (9 dyne/cm^2), 100 ml/min (6 dyne/cm^2), and 50 ml/min (3 dyne/cm^2) for 24 hours. The control group was subjected to similar incubation conditions without flow. The cells in the experiments remained attached and viable. All experiments were performed in triplicate or more.*

Results. *Shear stress significantly reduced ($p < 0.001$) the 24-hour incorporation of tritiated thymidine and cell proliferation. This effect was proportional to the level of shear stress and was still evident 24 hours after flow cessation. Results of flow cytometry confirmed a lower percentage of SMC in S phase with increasing shear stress. Synthesis of cell-associated proteins was increased twofold ($p < 0.01$) in SMC subjected to laminar flow. SMC subjected to shear stress released a higher quantity of mitogens, including a platelet-derived growth factor (PDGF)–like substance as detected by immunologic testing. Fifty percent volume per volume conditioned serum-free medium from SMC subjected to shear stress increased threefold the tritiated thymidine uptake in PDGF receptor–bearing Swiss 3T3 cells as compared with conditioned serum-free medium from control SMC not subjected to shear stress and twelvefold as compared with standard control. The release of mitogens was proportional to the level of shear stress and was still evident 24 hours after flow cessation. The mitogenic activity was partially reduced (30%, $p < 0.01$) by an excess of monospecific anti-PDGF antibody.*

Conclusions. *We conclude that (1) increasing shear stress inhibits SMC proliferation and stimulates the synthesis of cell-associated proteins and the release of mitogens and (2) decreasing shear stress facilitates proliferation of SMC. Thus, in situations of arterial flow separation, the increased release of mitogens from SMC subjected to high shear stress and the increased proliferation rate and susceptibility to mitogens of SMC subjected to very low shear stress may generate a critical condition that predisposes to the development of atherosclerosis with early plaque formation in regions of low-flow shear stress. (SURGERY 1993;113:691–9.)*

Impaired endothelial prostacyclin production of the canine vein graft in a poor distal runoff limb

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Background. *Because blood flow modulates endothelial prostacyclin production, the extent of this production in autologous vein grafts implanted in poor distal runoff limbs needed to be examined.*

Methods. *Endothelial prostacyclin production in canine autologous vein grafts was measured in poor distal runoff limbs (poor runoff group) and compared with findings in normal runoff limbs (control group). Vein grafts were perfused in a closed circuit at 3 days and 1, 2, 3, and 4 weeks after*

implantation; after perfusion for the first 30 minutes in a steady flow (basal prostacyclin production), the grafts were exposed to arachidonic acid (stimulated prostacyclin production) for the following 30 minutes. Prostacyclin, as the metabolite 6-keto-PGF$_{1\alpha}$ was radioimmunoassayed.
Results. *Basal and stimulated prostacyclin production increased in both groups during a period of time after implantation. At 2 weeks when endothelialization was complete, prostacyclin production in the poor runoff group was impaired, compared with the findings in the control group, and this difference increased with time. At 4 weeks the stimulated prostacyclin production was 18.91 ± 4.03 ng/cm^2 in the control group and 11.60 ± 1.67 ng/cm^2 in the poor runoff group ($p < 0.05$).*
Conclusions. *We propose that the impaired capacity of the vein graft to produce prostacyclin in a poor distal runoff may lead to loss of graft patency in reconstructed arteries. (*S*URGERY 1993;113:700–8.)*

Activation state of polymorphonuclear leukocytes in surgical patients: Characterization of surface receptor expression

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Background. *We studied the expression of chemotactic, opsonic, and adherent receptors on the membranes of polymorphonuclear neutrophils (PMNs) from surgical patients because modulation of these receptors has been suggested in the control of critical PMN functions that directly or indirectly influence patient outcome.*
Methods. *Healthy subjects who had PMN adherence, chemotaxis, and receptor measurements were compared with preoperative surgical patients and those who were within 48 hours of an admission to an intensive care unit (surgical intensive care unit) because of an acute illness.*
Results. *The following receptor/cell pattern was found in control subjects, preoperative patients, and patients in the surgical intensive care unit, respectively: formyl peptide (13,000 vs 18,000 vs 22,000), CR3 (59,000 vs 105,000 vs 121,000), fibronectin (21,000 vs 20,000 vs 35,000), FcIIγ (9,000 vs 20,000 vs 25,000), C5a (347 vs 265 vs 250 mean channel number), and FcIIIR (64,000 vs 75,000 vs 26,000). This receptor pattern was partly correlated directly or indirectly with the acute-phase response, neutrophil adherence, and PMN chemotaxis from these subjects.*
Conclusions. *The data suggest that there are alterations in the expression and modulation of PMN surface membrane receptors in patients with a "stable" disease process compa with those with an acute illness, which may affect critical PM functions needed to combat bacterial infections. (*S*URG 1993;113:624–30.)*

Incidence, structure, and function of enlarged parathyroid glands discovered accidentally during thyroi surgery

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Background. *Operation on rare patients with mainly a sev renal stone disease and considerably elevated urinary calciu excretion has substantiated the association of parathyro gland abnormalities with normocalcemia. This study exa ines incidence, structure, and functional characteristics enlarged parathyroid glands of patients with normocalcem scheduled for thyroid surgery.*
Methods. *Eleven enlarged parathyroid glands weighing 1 to 1000 mg were discovered in 9 (1.5%) of 594 patients wi normocalcemia undergoing thyroid operation. The preop ative total serum calcium concentration was 2.30 to 2. mmol/L and less than 2.38 mmol/L in four of the ni patients. Intact serum parathyroid hormone and alkali phosphatase levels were elevated in only one individual, an all patients showed normal serum creatinine values.*
Results. *All but three of the 11 enlarged parathyroid glan exhibited microscopic abnormality on routine histopatholog examination, including staining for cytoplasmic fat with red O. Immunohistochemical staining with a monoclon antibody recognizing the functionally important calciu receptor of the parathyroid cell surface and analysis of th calcium-regulated cytoplasmic Ca^{2+} concentration of disperse parathyroid cells substantiated that only a single gland 130 mg had no discernible functional abnormality.*
Conclusions. *The findings underline the diagnostic difficu ties of parathyroid histopathology and support the presence disturbed parathyroid hormone secretion even in norm calcemic patients with enlarged parathyroid glands. Th functional derangement of these glands substantiates th indication for their surgical excision even in patients exhibi ing midnormal serum calcium concentrations, although the possible contribution to the development of a clinically ove hyperparathyroidism can only be speculated. (*S*URGER 1993;113:655–61.)*

orrespondence

e future of vascular surgery

tter 1

agree with Mr Beard and Dr Gaines (*Br J Surg* 1993; **80**: 185–6) it vascular surgeons and radiologists should work together in tients' best interests and that the Vascular Surgical Society should p to promote this collaboration by changing its name to the Vascular ciety. There are, however, a number of points with which we take ue.

A modern trainee in vascular surgery should receive training in dovascular procedures, including angiography and angioplasty. ely there is no reason why such a trainee cannot be schooled in the evant radiation physics, equipment assessment and associated ects of safety? The need for vascular surgeons to perform giography and angioplasty depends on the availability of inter-ational vascular radiologists and, if there is a relative shortage of se consultants, we see no reason why a properly trained vascular geon should not perform these procedures.

It should be borne in mind that, with the advent of colour Doppler rasonography and magnetic resonance imaging, the role of giography in diagnosis may recede over the next few years and that only need for angiography may be as part of therapeutic angioplasty. agree that the best vascular service will be provided through a m approach but would suggest that there is no need for strict job lineations within the team and that the role of each member will pend on levels of expertise available among the team members. Why ould a patient be denied the chance of angioplasty by a properly ined vascular surgeon simply because it has been decided *ex cathedra* at this procedure should be performed only by vascular radiologists?

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e read with interest the article by Mr Beard and Dr Gaines regarding dovascular procedures (*Br J Surg* 1993; **80**: 185–6). As a vascular rgeon and a radiologist enjoying a close working relationship within large district general hospital, and having followed the debate on the sue at the meetings of the Vascular Surgical Society in London and e British Society for Interventional Radiology in Hull, we share their ncerns and their plea for a team approach to the management of scular disease.

Our practice involves an initial duplex scan to identify lesions itable for angioplasty, review of which enables angioplasty to be rried out at the same time as initial angiography in most cases. For ultisegment disease, this approach often reduces the need for traoperative angioplasty if additional revascularization is required. our hospital all intraoperative angioplasties are carried out as a joint rocedure between surgeon and radiologist. The procedure is scheduled ad the radiologist and scrub nurse are then incorporated into the perating team for the relevant part of the operation. This is not gistically difficult, and both teams find it mutually beneficial. We do ot see availability of radiological facilities as a major problem.

It would indeed be a pity if tribalism, which is not uncommon in e Health Service, were to stand in the way of improving the quality service provided to patients at a time when advances in the anagement of vascular disease have increased the therapeutic options vailable.

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Letter 3

Sir

In advocating a closer liaison between vascular surgeons and radiologists (*Br J Surg* 1993; **80**: 185–6), Mr Beard and Dr Gaines are wrong to claim that the traditional preserves of the Royal Colleges cut across the development of integrated vascular training, that vascular surgeons and radiologists risk relegation to the role of technologists, and that the Vascular Surgical Society is isolationist and should be reformed as a disease-based organization. Acknowledging that vascular surgeons should work closely with other medical specialists with an interest in vascular disease, I nevertheless feel that our Society should continue to have the advancement of vascular surgery as its primary aim. After all, who else can maintain high standards of vascular surgical practice and training?

It is vital that a strong vascular surgical voice is heard in the Joint Committee for Higher Surgical Training and the Specialist Advisory Committee in General Surgery. The Society represents nationally our views on the provision of vascular surgical services, and it relates internationally to sister societies in other countries. That is why, last November, when these issues were debated at the 26th Annual Meeting, a substantial majority of members voted to retain the 'surgical' title.

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Letter 4

Sir

The article by Mr Beard and Dr Gaines (*Br J Surg* 1993; **80**: 185–6) makes a useful contribution to the debate on the future of vascular surgery but a number of points warrant correction or comment.

First, a recent survey undertaken by the Vascular Surgical Society of Great Britain and Ireland showed that the number of consultants with a vascular surgical interest increased by 33 per cent between 1988 and 1992. As a consequence there are now 2·37 vascular surgeons per 500 000 people, which exceeds slightly the ratio recommended by the Vascular Advisory Committee (VAC) in 1988. (The VAC is a committee of the VSS not The Royal College of Surgeons of England.)

Second, the article gives a misleading account of the Society's review of training in endovascular procedures. The recommendations of the VAC working party were for internal debate only, and it was never intended that they should be published without prior consultation with radiological colleagues. With agreed amendments these recommendations form the basis of a consensus document soon to be published that has been endorsed by the respective Presidents on behalf of the VSS, the British Society for Interventional Radiology and The Royal Colleges of Surgeons and Radiologists.

Third, there is little doubt that the future management of patients with vascular disease will be a team affair; this is surely a trend to be encouraged. A group of people contributing individual skills towards the achievement of common objectives is an ideal worth striving for, but strict demarcation between roles is more likely to be obstructive than helpful. Endovascular procedures, for example, are quite rightly regarded as being primarily within the province of interventional radiology, but under certain circumstances it may be appropriate for them to be undertaken by surgeons. Radiologists should not feel threatened by this practice, and it is to be hoped that they will offer assistance to ensure that surgeons receive adequate training in wire and catheter techniques.

Finally, it is axiomatic that 'the team' must meet together regularly at unit level, and it follows that there is a need also for interdisciplinary meetings on a national scale. A proliferation of narrow-interest societies meeting separately and without direct regular communication would be disastrous.

Given the established position and tradition of the VSS as the principal professional organization in the UK and Ireland concerned with vascular disease, it is appropriate that it should provide the forum for interdisciplinary discussion and debate. Mr Beard and Dr Gaines express the view that to fulfil this role effectively the Society must modify its construction and change its name to make it more acceptable to non-surgical specialists. The revisions proposed by these authors were debated by the VSS at the 1992 Annual Meeting but were rejected by a large majority. This decision was certainly not intended as a rejection of radiologists, other clinicians and scientists whose attendance and participation in the scientific meetings of the Society are universally supported.

Most members of the VSS believe non-surgeons to be already adequately accommodated within the present constitution and are reluctant to accept change that could fundamentally alter the character of the Society. Concern remains that, unless non-surgical specialists are offered membership of the Society on equal terms, their unreserved support is unlikely to be forthcoming.

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Choice of agent for peripheral thrombolysis

Sir

The article by Mr Earnshaw and colleagues (*Br J Surg* 1993; **80**: 25–7) presented many data but provided no answers. The authors stated that it was not possible to show that tissue plasminogen activator (tPA) was superior to streptokinase for peripheral thrombolysis, but admitted in their discussion that there are difficulties in interpreting non-randomized studies such as theirs. This problem is compounded by the fact that their two groups were not comparable in terms of duration of ischaemia, incidence of critical ischaemia and cause of thrombosis, with a greater number of thrombotic occlusions and fewer postangioplasty occlusions in the group receiving tPA. The last also reflects the fact that the tPA and streptokinase treatments were carried out at different times.

The median duration of lysis in this study was 22 h for tPA and 18 h for streptokinase, but the range of the duration of treatment required is not given and the average duration of lysis for streptokinase usually reported[1,2] is considerably longer than 18 h. The authors also reported a high incidence of major complications (22 per cent) in patients receiving tPA, despite a rather low dose (0·5 mg/h) being used. This figure is much higher than other authors have reported using comparable dose regimens[3].

The authors stated that the limb salvage rate was similar in both groups, although in patients receiving tPA critical ischaemia with neurosensory loss was present in nine of 23 limbs compared with only five of 20 in those given streptokinase. Of the 20 limbs receiving streptokinase, seven underwent amputation (presumably major – not stated by the authors), while in the tPA group only four of 23 had amputation. Four patients given tPA died (cause not specified), decreasing the limb salvage rate in this group. The series is also non-contemporaneous, leaving even more scope for problems of interpretation.

It will need more than non-randomized retrospective studies using non-comparable small groups of patients receiving tPA and streptokinase to convince vascular surgeons and radiologists that tPA is no better than streptokinase in the face of much other literature, quoted by the authors, to the contrary.

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Authors' reply

Sir

The price of the thrombolytic agent is but a small proportion of t overall admission cost of a patient with acute leg ischaemia. Howev radiology managers are finding tissue plasminogen activator (tP costs looming ever larger in their budgets and need to be convinc of its superiority over streptokinase. Messrs Andaz and Shields a correct that there is indirect evidence of the superiority of tPA. It w this evidence that persuaded me to encourage the radiologists in Bris to change to tPA for a limited period. Careful audit of this chan failed to find evidence that tPA was superior for the reaso documented. Prospective audits sometimes unkindly emphasi complication rates. Improvements in other series may derive fro increasing experience in individual units.

It is to our shame that few randomized trials have been performe but the difficulties of standardizing methods and enrolling patients in studies of acute leg ischaemia should not be underestimate Radiologists and surgeons have recently formed the Thromboly Study Group through which it is hoped collaborative trials can undertaken. Further information about the Group may be obtain from Mr D. C. Berridge (Secretary), The Freeman Hospital, Newcast upon Tyne NE7 7DN, UK. It is only through proper randomiz comparison of thrombolytic agents and other surgical techniques th the answers for optimal treatment of acute leg ischaemia, which we seek, can be provided.

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Selective cholangiography in laparoscopi cholecystectomy

Sir

We read with interest the article by Mr Grace and colleagues o cholangiography in patients undergoing laparoscopic cholecystectom (*Br J Surg* 1993; **80**: 244–6). The authors concluded that routi radiography of the biliary tree is unnecessary, although variations i biliary anatomy are reported in as many as 15 per cent of individuals[1].

A recent North American study has shown that endoscop retrograde cholangiopancreatography before conventional electiv cholecystectomy is of no advantage[2], even if duct stones are suspecte On the other hand, operative cholangiography is time consuming an bile duct injuries often occur early in the dissection around the cysti duct, before cholangiography is performed. However, common bil duct injuries during laparoscopic cholecystectomy are not infrequen especially in the surgeon's first laparoscopic procedures[3]. Thus, it i surprising that the article by Mr Grace and colleagues makes n mention of intravenous cholangiography (IVC). Several studies hav shown that the clarity of imaging of the biliary tree with IVC is excellen and compares favourably with that of operative cholangiography[4–7] IVC can be easily performed as an outpatient procedure in an radiology unit and has therefore been popular for many years Unfortunately, during the 1980s IVC was nearly abandoned[7] becaus of reported poor imaging and a high incidence of allergic reaction The contrast medium currently employed (at the proper infusion rate is safe[8], and the association of tomography further improves the qualit of imaging. We therefore think that IVC represents an optima cost–effective diagnostic tool to assess the anatomy of the biliary tre before operation. It should be performed in all patients planned fo laparoscopic cholecystectomy and is mandatory in a surgeon's firs laparoscopic procedures.

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Managing swabs in the operating theatre: a new method

Sir

The letter from Mr R. A. L. Young (*Br J Surg* 1993; **80**: 399) xpounding the benefits of eliminating swab counts as observed in Heidelberg would, if heeded, introduce a practice hitherto regarded as negligent. Such a routine was practised in a busy New York hospital in the 1960s where it had been regarded as the norm. Four lawsuits in a 2-year period resulted in very large settlements for damages. Two were for small swabs left one each in the abdomen and chest. One was or a large pack left intra-abdominally in a large woman and eventually emoved elsewhere 2 years later from within the colon whence it had migrated causing obstruction (this phenomenon is well documented). The fourth was for a 7" artery clamp found 4 months later in the pelvis ollowing gastrectomy. The hospital rapidly adopted the practice of counting swabs and instruments and has wisely continued this elementary safeguard since.

Although some traditional surgical practices, such as the wearing of face masks, may justifiably be reassessed, the abandonment of basic afety precautions is an invitation to disaster irrespective of savings in money or time.

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Easy technique for cholangiography during laparoscopic cholecystectomy

Sir

We read with interest the description by Mr Hunter and colleagues of their technique for cholangiography during laparoscopic cholecystectomy (*Br J Surg* 1993; **80**: 211). We also perform routine cholangiography in all patients who have not undergone endoscopic retrograde cholangiopancreatography. We similarly use a 5-Fr ureteric catheter but would suggest that the Twohy needle (Rocket of London, Watford, UK) has important advantages compared with the Tilley–Lichtwitz trocar and cannula.

First, it is considerably longer: 20·5 *versus* 8 cm. This extra length allows the Twohy needle to enter the abdomen and be placed alongside the cystic duct even in obese patients. A small hole is then made in the cystic duct into which the tip of the Twohy needle or protruding ureteric catheter is inserted.

Second, the angled tip of the Twohy needle gives greater scope for manipulating the ureteric catheter into a small cystic duct. If the duct is of reasonable size, such that the tip of the Twohy needle can be inserted into it, this angulation helps prevent the catheter snagging on cystic duct valves.

The ureteric catheter is fixed in position with a clip, which is tightened slowly until passage of fluid through the catheter is just prevented. Release of pressure on the clip at this point allows contrast medium through the catheter but prevents leakage. Injection of contrast is facilitated by a Luer–Lok connector on the end of the ureteric catheter, which enables a syringe to be attached directly. We have now been using this technique routinely for 2 years and have experienced no complications.

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Adjuvant herbal treatment for gallstones

Sir

We read with interest the Case Report by Mr Savage and colleagues (*Br J Surg* 1992; **79**: 168) concerning emptying of the gallbladder of stones after herbal treatment. The following case illustrates that such treatment may have important surgical consequences.

A 58-year-old man presented with a history suggesting recurrent attacks of gallstones. Ultrasonography confirmed the diagnosis. As he had a marginally raised serum alkaline phosphatase level, endoscopic retrograde cholangiopancreatography (ERCP) was performed. This demonstrated multiple small stones in the gallbladder; the bile ducts were free from stones. The patient was admitted for elective laparoscopic cholecystectomy 4 weeks later. He had had no symptoms suggesting bile duct stones in the intervening period and liver biochemistry was normal. At laparoscopic cholecystectomy, operative cholangiography revealed, to our great surprise, ten to 15 small stones in the common bile duct. The operation was converted to an open procedure and the gallbladder and common duct stones removed. The gallbladder was entirely empty of stones.

At direct questioning after operation the patient stated that he had, of his own accord, taken a herbal medicine to treat his stones in the period between ERCP and operation. The medicine contains 11 different herbs (details are available from the authors).

Surgeons should be aware that various herbal medicines can cause the gallbladder to empty its stones into the bile duct, and that recent normal ERCP does not preclude the presence of stones in the bile duct at the time of operation in patients who have taken such medicine. This fact should be recognized by those arguing against operative cholangiography as a routine procedure.

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Autotransplantation of splenic tissue in an isolated segment of small intestine

Sir

Dr Shokouh-Amiri and colleagues recently reported experiments on the autotransplantation of splenic tissue in pigs (*Br J Surg* 1992; **79**: 1327–9). Splenic autotransplantation is an interesting field of research[1] and many important questions concerning the regeneration of autotransplanted splenic tissue are of basic scientific and major clinical relevance[2].

Is the paper of Dr Shokouh-Amiri and colleagues a real step forward? They implanted splenic tissue in an isolated segment of the small intestine. Will this technique be accepted by the surgeon in a clinical situation? What are the advantages of the small bowel compared with other locations? The authors documented only the weight of the transplants, which was comparable to that for other sites. There were no functional studies of blood flow or clearance, no morphometry and no immunohistology. Such studies have been performed by others[3,4] and were reviewed recently[2]. Why did the authors not quote the excellent reviews on splenic autotransplantation and postsplenectomy sepsis recently published in this Journal[5,6] but refer to older papers? New insight into the complexities of splenic regeneration will be gained only by combining quantitative morphometric data with analysis of the clearance and immune function of autotransplanted splenic tissue[2]. This is surely the best approach to find a way to prevent postsplenectomy sepsis in patients.

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Authors' reply

Sir

We appreciate the comments of Drs Pabst and Westermann and thank you for the opportunity to reply. Although we agree that splenic autotransplantation is an interesting field of research and that quantitative morphometric parameters with tests on clearance and immune function of autotransplanted splenic tissue are the main indices that should be investigated, we would draw their attention to the following. An ideal site for splenic autotransplantation is yet to be found. Our pilot study was part of an ongoing project that intends to find the site that gives the best function of the regenerated splenic implants. If further functional, morphometric and immunohistological studies (which we hope will be carried out in laboratories other than our own) show that regenerated tissue implanted in isolated small bowel segments is functional, then this site will be a useful addition to the field of splenic autotransplantation. Like omental implants, regenerated tissue implanted in isolated small bowel segments drains to the portal circulation. Implants at this site will theoretically induce fewer adhesions, which is a real concern in patients with omental implants[1], since they are contained in a closed sac with a smooth surface. If further studies prove the suitability of this site for implantation, this technique will be considered by surgeons since the preparation of an isolated bowel loop and implantation of splenic slices into it adds no more than 10 min to the operating time; these intestinal procedures are also familiar to most surgeons. Furthermore, since the ability of splenic tissue to regenerate in one site is limited, it may be advantageous to implant as much splenic tissue as possible at different locations.

We preferred to cite original papers in our work since in the reviews mentioned by Drs Pabst and Westermann the most recent references are from 1989 and 1986 respectively.

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1. Ben C, Echun D. Regeneration of the spleen and splenic autotransplantation. *Br J Surg* 1991; **78**: 1276 (Letter).

Benign parotid cysts associated with human immunodeficiency virus infection

Sir

We read with interest two recent articles on human immunodeficienc virus (HIV)-related benign lymphoepithelial cysts. The first was 2-year surgical audit of parotid disease in HIV-infected patients i Lusaka, Zambia, by Dr Bem and colleagues (*Br J Surg* 1992; 79 768–70) and the second was a Case Report by Mr Barr and associate (*Br J Surg* 1993; **80**: 39). The Zambian study discussed the presentatio and management of six lymphoepithelial cysts, four parotid and tw extraparotid. The second paper reported one parotid lymphoepithelia cyst, discussing presentation, diagnosis and management.

We would like to report our experience over a 2-year period a St Mary's Hospital, London, where we have managed 12 HIV-positiv patients with lymphoepithelial cysts. There were two women, though to have contracted HIV following blood transfusion while living i Africa, and the remainder of the patients were male homosexuals. Th average age was 38 (range 28–53) years, and three patients ha diagnoses defining acquired immune deficiency syndrome. Thre patients had extraparotid and nine parotid disease, four of whom ha bilateral involvement.

All lesions were subjected to fine-needle aspiration cytolog (FNAC), which showed characteristic features of lymphoepithelia cysts with no evidence of malignancy. Four patients underwen computed tomography (CT), which revealed multiple homogeneou cystic masses. Ultrasonography in three patients showed cystic lesions Two patients underwent surgical excision, one superficial parotidectomy and the other cyst enucleation.

We believe that operation should be avoided in this group o high-risk patients. Diagnosis can be made by FNAC, in combinatio with ultrasonography or CT. We realize that this plan may not b possible in countries such as Zambia where there are limited cytologica and CT services.

Treatment should involve conservative management, either by leaving the cysts alone with regular follow-up or by repeated aspiration in the outpatient department; recurrence is common after 6 weeks. We are currently evaluating infusion of tetracycline into cysts to induc sclerosis and prevent recurrence.

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Ankle fracture is associated with prolonged venous dysfunction

Sir

We read with interest the paper by Mr Burke and colleagues (*Br J Surg* 1993; **80**: 36–8), in which reduced venous calf muscle pump activity as measured by air plethysmography was noted after ankle fracture uncomplicated by deep vein thrombosis. The measurement of venous calf muscle pump activity was made by performing a simple standard series of exercises. The major parameters that showed a difference after ankle fracture were ejection fraction and residual volume fraction (RVF). It is not clear from the paper whether these tiptoe manoeuvres were standardized either in the height achieved with each exercise or the force exerted with each manoeuvre. Surely it is likely that patients, when asked to tiptoe ten times, will take more of their weight on the unaffected side when they have recently sustained an ankle fracture. This point was mentioned in the discussion but could have been made with greater certainty if the force and excursion of each tiptoe manoeuvre had been measured.

The measurement of RVF has been shown in one paper[1] to correlate well with ambulatory venous pressure (the 'gold standard' test of venous function) and has therefore been used here without venous pressure measurement. We have shown[2] in 103 limbs with different degrees of venous insufficiency a Spearman correlation coefficient of only 0·03 tween ambulatory venous pressure and RVF, suggesting that the loption of the latter as a substitute for ambulatory venous pressure easurement is not justified.

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Christopoulos D, Nicolaides AN, Galloway JM, Wilkinson A. Objective noninvasive evaluation of venous surgical results. *J Vasc Surg* 1988; **8**: 683–7.

Payne SPK, Thrush AJ, London NJM, Bell PRF, Barrie WW. Venous assessment using air plethysmography: a comparison with clinical examination, ambulatory venous pressure and duplex assessment. *Br J Surg* 1993 (in press).

uthors' reply

ir

hank you for the opportunity to reply to the points raised by r Payne and colleagues. Our paper documented the overall effects f ankle fracture on calf venous pump function and did not attempt separate out the relative contributions of pain, immobilization and weight bearing. Patients were asked to perform the tiptoe movement taking as much weight as was tolerable on the injured side. We did not attempt to standardize the height or range of the ankle joint movement, but instead attempted to mimic the degree of venous pump function that the patient was likely to be achieving when walking unsupervised outside the laboratory setting.

Although part of the reason for the reduced ejection volume fraction (EVF) and consequent increased residual volume fraction (RVF) may have related to an inability of the patient to bear weight, this was unlikely to have been the only cause as EVF and RVF were still altered at 12 weeks (at which stage the patient had already been weight bearing for 6 weeks after cast removal). We agree that careful evaluation of the various individual factors contributing to muscle pump function would now be appropriate.

We are interested to see that the Leicester group found a poor correlation between RVF and ambulatory venous pressure in their laboratory. We do not feel, however, that this makes our findings of reduced venous calf pump function any less relevant as a contribution towards understanding the aetiology of lower-limb swelling following ankle fracture.

S. Tierney
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P. Fitzgerald
T. O'Sullivan
P. A. Grace
D. Bouchier-Hayes

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Publisher's announcement

Change of address

The address of the Editorial Office of *The British Journal of Surgery* has changed. With effect from 1 July 1993, all correspondence and queries relating to the Journal should be directed to:

The British Journal of Surgery
Blackwell Scientific Publications
25 John Street
London WC1N 2BL
UK

Telephone: +44 (0)71 404 4101
+44 (0)71 404 1831 (direct line)
Facsimile: +44 (0)71 404 1927

Those who have just written to our previous address in London are assured that mail arriving there after 30 June 1993 will be forwarded.

Book reviews

Endoscopic Retrograde Cholangio-pancreatography: Technique, Diagnosis and Therapy

J. H. Siegel. 286 × 223 mm. Pp. 426. Illustrated. 1992. New York: Raven Press. £132·95.

What a joy to encounter this well written and exceptionally well illustrated book. It contains first-class radiology of endoscopic retrograde cholangiopancreatography (ERCP) including good examples of normal anatomical variation as well as a wide range of pathology. In addition, there are superb endoscopic photographs and good line drawings. The book is clearly written by an expert in the field and it acts as a first-class introduction as well as a valuable text in which problem solving is emphasized. The chapter on endoscopic sphincterotomy is excellent in this respect and it is valuable to encounter the considerable volume of personal data that is included. Of special merit is the almost unique experience of the relatively uncommon condition of sclerosing cholangitis and the good results of endoscopic stenting in affected patients.

The chapter on sphincter of Oddi dysfunction is rather limited and could not be regarded as a good overview. The discussion of the expanding field of ERCP and its involvement in complications of laparoscopic cholecystectomy is quite limited. In addition, there is little mention of the newer stainless steel expanding stents that have become available recently. Jerome Siegel acknowledges this deficiency and will doubtless correct the few weaker areas in a future edition. These sections slightly date what is otherwise an excellent publication. We have here a landmark book that is, in this reviewer's opinion, essential to every doctor beginning or established in this enlarging clinical sphere.

C. W. Imrie

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Baillière's Clinical Gastroenterology – Portal Hypertension

R. Shields (ed.). 232 × 154 mm. Pp. 634. Illustrated. 1992. London: Baillière Tindall. £27·50.

This small book in the *Clinical Gastroenterology* series keeps up the high standard of its predecessors. The guest editor has drawn together contributions by experts in the field of portal hypertension from around the world. In view of this international flavour it is a pity that it does not include at least one chapter on schistosomiasis, the world's largest cause of portal hypertension. This is a minor criticism of an otherwise excellent book that presents a succinct and easily readable appraisal of new thinking in this field. The old problem of the place, if any, of prophylactic therapy is well discussed, although logically it might have appeared earlier in the book rather than near the end. Sclerotherapy is well documented for both acute and chronic indications. However, in the chapter on gastric varices the authors state that there is *little* role for prophylactic sclerotherapy. Since, as they state, gastric varices are 'covered by relatively thick gastric mucosa', it would be wiser to say there is *no* role, to avoid the risk of postinjection ulcers destroying this previously intact protective layer. Shunt surgery is not yet dead and I am happy to see it dealt with in a logical and practical manner. The case for transplantation in patients with Child's grade C disease is well made, although obviously most countries do not have this facility readily available. For oesophageal transection and devascularization procedures it is reasonable that the contribution should come from Japan, where there is considerable experience in this field. However, one must be careful with translating such results westward, since 30 per cent of Japanese with cirrhosis so treated had never bled; additionally, many patients suffered from non-cirrhotic portal hypertension. This book will be welcomed by all interested in the field of portal hypertension as an excellent volume containing many up-to-date references.

G. W. Johnston

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Colon and Rectal Surgery. 3rd ed.

M. L. Corman (ed.). 260 × 207 mm. Pp. 1328. Illustrated. 199 Philadelphia, Pennsylvania: J. B. Lippincott. £175.

The third edition of *Colon and Rectal Surgery*, edited by Marvin I Corman, is almost one-third longer than its predecessor an incorporates more illustrations, some in colour. This is now comprehensive and up-to-date textbook of coloproctology.

There are expanded sections on endoscopy and surgical stapling The physiology section has been revised and gives an excellent summar of current understanding of the role of new investigative techniques in clinical practice. The management of colorectal cancer receive extensive coverage while ulcerative colitis and Crohn's disease are now dealt with in separate chapters. The non-fashionable but clinicall difficult topics of pruritus ani, anorectal malformations and cutaneous conditions are clearly presented; these sections will be particularl useful. The book is presented in a style that is easy to read. It is ver much a practical user's guide, reminiscent of Goligher's famous textbook.

It is immediately evident on reading this book that the difference between UK and North American surgical practice, particularly in coloproctology, have largely disappeared. Indeed, this text could be described as 'mid-Atlantic' in approach, an aspect that is emphasized by the extensive referencing of European work. In all, this is an excellen book that would be of value to any clinician interested in coloproctology.

I. G. Finlay

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Operative Manual of Endoscopic Surgery

A. Cuschieri, G. Buess and J. Périssat (eds). 274 × 196 mm. Pp. 353 Illustrated. 1992. Heidelberg: Springer. DM296.

Three of the European pioneers of minimally invasive surgery have collaborated to edit this beautifully illustrated volume. It ranges widely through the history of minimally invasive surgery, equipment and techniques. There is even room for a short debate on the relative merits of the term 'minimally invasive' as opposed to 'minimal access' surgery A striking feature of the book is the wealth and quality of the illustrations, both clinical photographs and, particularly, the line drawings. The video system and instruments are described in detail with great clarity. The breadth of scope of the book is illustrated by chapters on setting up a minimally invasive surgical unit and on training methods. The account of the basic surgical procedures including dissection, haemostasis, knotting and suturing is particularly valuable.

The bulk of the book is devoted to descriptions of individual procedures but some details of technique will not find general acceptance. For example, the use of a nasogastric tube and urinary catheter for laparoscopic cholecystectomy and the continental use of the Lloyd-Davies position have not found favour elsewhere in the world. For appendicectomy, the suggestion that the appendix stump should be dabbed with antiseptic, that antibiotics should not be used before operation but should be given after surgery for 5 days, and the use of a drain for 3–5 days will not find favour with most British surgeons. The chapter on laparoscopic hernia repair is disappointing, concentrating on the technique of simple closure of the internal opening, which is now generally discredited. There are two surprising omissions: a technique of thoracoscopic oesophagectomy (described by Professor Cuschieri) and laparoscopically assisted colonic resection.

It is appropriate in this rapidly advancing field that the book should end with a chapter on future advances in endoscopic surgery. Developments in stereoscopic and three-dimensional television systems, shape memory alloys and remote handling techniques offer a glimpse into the future. At £88·50 this book is priced more for the department or library than the individual but is highly recommended to all surgeons practising in this area.

I. M. C. Macintyre

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he Impact of HIV on Surgical Practice

. Wastell and J. P. S. Cochrane (eds). 238 × 170 mm. Pp. 91. lustrated. 1992. London: Royal College of Surgeons of England.

his is the first book of a new series called *Studies in Surgery* published y The Royal College of Surgeons of England and based on a conference ld there. The book is a transcription of the talks given; it has ndergone minimal editing to 'preserve the atmosphere of the onference and liveliness both of presentation and discussion'. After an troduction by the President of the College there are 17 'talks' divided to three sections dealing first with an update on human mmunodeficiency virus (HIV), the virus and acquired immune eficiency syndrome, second with practical considerations, and third ith ethical issues. The discussion relating to a talk or section is cluded.

The book is not a literary masterpiece; the English is 'spoken' rather han 'written', there are many textual errors and there are consistencies in the style of printing and presentation (although the uality of the colour plates is excellent). It is, however, easy and fun read. If this material were further edited or rewritten it could lose s freshness and some of its value. The speakers have presented papers at are thoughtful and thought provoking; they do not pretend to ave all the solutions either in their formal presentations or in their swers to questions. The liveliness of the meeting comes through well some of the discussions; one of my favourite exchanges comes from junior surgeon who 'cannot identify anyone who is actually looking ter his interests'.

As HIV becomes a more regular part of surgical thinking, some of e original questions (Which patients should be tested?) remain and me newer ones (What to do with the HIV-positive healthcare orker?) are evolving. Discussion of these is essential and this book rovides the opportunity for readers to hear the views of a group who e particularly interested in finding the answers. As a record of the resent state of thinking this is a valuable historical text.

This is a living book that is enjoyable to read. I would recommend to anyone who, in addition to being informed, wants to think about e impact of HIV on surgical practice. The Royal College of Surgeons f England should be pleased with the first volume in this new series.

A. J. W. Sim

nited Arab Emirates University
l-Ain
nited Arab Emirates

Atlas of General Surgical Technique

F. E. Rosato and D. J. Barbot (eds). 314 × 254 mm. Pp. 400. Illustrated. 1992. London: Gower Medical. US$187.

This book is beautifully produced and could be recommended for any library or indeed as a gift for a junior surgical registrar. However, it is probably not detailed enough for old-timers or specialists. It presents a compendium of surgical procedures collected by specialists at the Jefferson Medical College department of surgery, and is 'primarily geared' for the surgical resident. By the authors' own admission they have not covered everything but the range is still comprehensive, spanning topics from endocrine to renal and liver transplantation surgery, and from gastrointestinal to thoracic procedures. As the book is most suitable for junior residents, it is a pity that there is no introduction outlining the principles of surgery; the absence of a section on urology also detracts from its usefulness to juniors on this side of the Atlantic.

Each chapter is introduced with a brief statement about surgical anatomy, indications for operation, anaesthesia, positioning of the patient and preparation. These are usually concise and apt – particularly in the section on thoracic incisions – but occasionally extend beyond the brief of the book, such as in the section on breast cancer. However, the main thrust of each section deals with the surgical technique of specific operations. The coloured line drawings are beautifully clear, abundant and often enhanced by well produced photographs. The text is clearly written but the pictures do not always match the pages of the script, which is a little tiresome for lazy readers. With so many changes occurring in surgical technique it would be hard for this kind of book to remain relevant. However, the authors do describe up-to-date techniques, including laparoscopic cholecystectomy, needle localization of breast lesions, hepatic assessment by intraoperative ultrasonography and, of course, renal and liver transplantation.

Small criticisms include problems of emphasis. I thought the section on haemorrhoidectomy and fissure *in ano* too short; central duct excision in the breast was described but not microdochectomy; the section on bile duct drainage does not include drainage of the segment III duct and, finally, I was not completely happy with the methods of identifying the seventh nerve in parotidectomy. However, all in all, I am very glad to have this book in my possession.

F. B. V. Keane

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Editors' announcement

Case Reports

It is the policy of the Editorial Board of the Journal to limit strictly the number of Case Reports that appear in each issue. During recent months we have been inundated with Case Reports; consequently there has been a very high rejection rate. We remain interested in receiving Case Reports of particular novelty or rarity, but brevity is another criterion of increasing importance. Contributors should note that a succinct Case Report can be used to fill a page that would otherwise be largely empty. To meet this requirement, it has proved necessary to tighten the existing guidelines for Case Reports. From now on they should be no more than 400 words in length or no more than 300 words if a figure is included. The existing limit of five references remains. We strongly encourage contributors to observe these new guidelines so as to avoid automatic rejection of their Case Reports.

R. C. N. Williamson
J. R. Farndon
J. A. Murie
C. D. Johnson

Notices and announcements

1–3 September 1993
4th International Congress – International Organization for Statistical Studies on Diseases of the Oesophagus
Paris, France
Information: Michele Liegeon, 2 Boulevard de Montparnasse, 75 015 Paris, France

2–4 September 1993
Second International Workshop: Inflammatory Bowel Disease
Treviso, Italy
Information: Dr G. Di Falco, Divisione Chirurgica III, Ospedale Regionale Generale 'Ca' Foncello', 31 100 Treviso, Italy

3–4 September 1993
Recent Developments in Immunology: Potential Clinical Impact on Surgery and the Treatment of Infection
Würzburg, Germany
Information: Professor A. Thiede, Josef-Schneider-Straße 2, W-8700 Würzburg, Germany

7–10 September 1993
6th International Congress on Interventional Ultrasound
Copenhagen, Denmark
Information: Dr C. Nolsøe, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

10–11 September 1993
Frontiers in Transplantation and Medical Treatment of Liver Disease
Hamburg, Germany
Information: Marion Schemnitzer, Master-Media GmbH, Bodelschwinghstraße 17, D-2000 Hamburg 63, Germany

12–16 September 1993
6th World Meeting on Impotence
Singapore
Information: Secretariat 6th WMI, Department of Obstetrics and Gynaecology, National University Hospital, Lower Kent Ridge Road, Singapore 0511

14–17 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

15–17 September 1993
Nottingham European Organization for Research and Treatment of Cancer Joint Breast Cancer Meeting
Nottingham, UK
Information: Mrs Wendy Bartram, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

29 September to 1 October and 2 October 1993
Principles of Colon and Rectal Surgery, and Biofeedback for Pelvic Floor Disorders/Endorectal Ultrasonography
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue South-east, Minneapolis, Minnesota 55414, USA

17–23 October 1993
Surgery of the Liver, Biliary System and Pancreas
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

1–5 November 1993
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

18–19 November 1993
Vascular Surgical Society of Great Britain and Ireland Annual Meeting
Manchester, UK
Information: Mr P. L. Harris, VSS Secretary, Link 8c, The Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

30 November to 2 December 1993
Eighth International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr S. C. S. Chung, Combined Endoscopy Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

23–28 January 1994
18th International Congress of Radiology
Singapore
Information: 18th ICR '94, Kent Ridge, PO Box 1052, Singapore 9111

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Depar ment of Anaesthesia and Operative Intensi Care, Klinikum Steglitz, Hindenburgdam 30, 12 203 Berlin, Germany

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Education Foundation, Department of Continuin Education, 9500 Euclid Avenue, Clevelan Ohio 44 195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians Universität Munich, Klinikum Großhader Chirurgische Klinik, Marchioninistraße 1 D-8000 Munich 70, Germany

20–22 April 1994
Association of Surgeons of Great Britai and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association o Surgeons, The Royal College of Surgeons o England, 35–43 Lincoln's Inn Fields, Londo WC2A 3PN, UK

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua d Ouvidor 60/414, 20 040-030 Rio de Janeiro Brazil

2–7 October 1994
World Congress of Gastroenterology
Los Angeles, California, USA
Information: World Congress of Gastroenterology Secretariat, 655 15th Street, NW Suite 300, Washington, DC 20 005, USA

6 November 1994
XXIX World Congress of the Internationa College of Surgeons
London, UK
Information: Jacqueline Webber Associates, 22 Park Farm Road, Kingston upon Thames, Surrey KT2 5TQ, UK

19–22 November 1994
XIXth European Society for Medical Oncology Congress
Lisbon, Portugal
Information: Secretariat, ESMO, Via Soldino 22, 6900 Lugano, Switzerland

nstructions to authors

he British Journal of Surgery publishes original articles, views and leading articles. Short notes, case reports and rgical workshops are also accepted. All manuscripts are bmitted to editorial review.

n article is reviewed for publication on the understanding that e work it reports has not been submitted simultaneously to nother journal, has not been accepted for publication sewhere and has not already been published. **Any detected tempt at dual publication will lead to automatic rejection and ay prejudice acceptance of future submissions.** Articles and eir illustrations become the property of the Journal unless ghts are reserved before publication. The title page should dicate if the paper is based on a previous communication a society or other meeting. Authors are requested to send ree copies of original articles and other editorial matter : The Senior Editor, *The British Journal of Surgery*, lackwell Scientific Publications Ltd, 25 John Street, London CIN 2BL, UK. Telephone: 071-404 1831. Facsimile: 71-404 1927.
ooks for review should be sent to the same address.

covering letter must accompany all submissions and must be gned by all authors. The covering letter should state if an bstract of the work has been published and whether the uthors wish the manuscript and/or illustrations to be returned the work is not accepted. The first named author is responsible r ensuring that all authors have seen and approved the anuscript and are fully conversant with its contents.

ejected manuscripts will not be returned to the authors, unless is is specifically requested.

thics

he Journal publishes all material relating to human vestigation and animal experiments on the understanding that e design of the work has been approved by local ethical ommittees or that it conforms to standards currently applied in e country of origin. The Journal further reserves the right ot to publish an article on the grounds that appropriate ethical r experimental standards have not been reached. Written onsent must be obtained from the patient, legal guardian or xecutor for publication in *The British Journal of Surgery* of ny details or photographs which might identify an individual. vidence of such consent should be submitted with the anuscript.

reparation of manuscripts

he British Journal of Surgery subscribes to the policy of niform requirements for manuscripts which is designed to ermit authors to resubmit papers to journals without extensive ecasting. Authors are advised to consult the *British Medical ournal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 988; **108**: 258–65, or to obtain the leaflet 'Uniform equirements for Manuscripts Submitted to Biomedical ournals' from The Editor, British Medical Journal, BMA ouse, Tavistock Square, London WC1H 9JR, UK (cost £1·00 er copy).

uthors are responsible for the accuracy of their report ncluding all statistical calculations and drug doses. **When uoting specific materials, equipment and proprietary drugs, uthors must state in parentheses the name and address of the anufacturer.** Failure to do so will result in delay in publication s the Journal considers that this information is essential for ny reader who wishes to obtain similar material. Generic ames should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery.* These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Referen to abstracts from meetings is discouraged; reference unpublished communications is not acceptable. Person communications should be cited in the text, in parentheses. T first author is responsible for confirming the acceptability the material quoted with the originator.

In the text, references should be numbered consecutively superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figur should be numbered in sequence according to the first mentio of the table or figure in the text. The sequence for a standar journal article should be: author(s); title of paper; journ name abbreviated as in Index Medicus (written in full if abbreviation quoted) and year of publication; volume numbe page numbers. For example: De Bolla AR, Obeid M Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 198 **66**: 184–6. The sequence for the chapters of a book should b author(s); chapter title; editors; book title; place publication; publisher; year of publication; page number For example: Calenoff L, Rogers L. Esophageal complicatio of surgery and lifesaving procedures. In: Meyers Ghahremani G, eds. *Iatrogenic Gastrointestinal Complication* New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical materia authors should consult *The British Journal of Surgery* 1991 **78**: 782–4. The Editors and statistical referees in evaluating manuscript will consider the *design* of the study, t *presentation* of the data, the *analysis* of the data, and t *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, shoul identify the primary and secondary hypotheses, and shoul explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used illustrate the main findings of a study. The use of standar deviation and standard error should be clearly distinguishe The use of the '±' symbol should be avoided; these statisti should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods we used for which analyses, and any methods not in common usa should be supported by references. Results of statistical tes should be reported by stating the value of the test statistic, t number of degrees of freedom and the *P* value. For exampl '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual *P* valu should be reported, to two decimal places, especially when t result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses shoul be reported using confidence intervals instead of, or in additio to, *P* values.

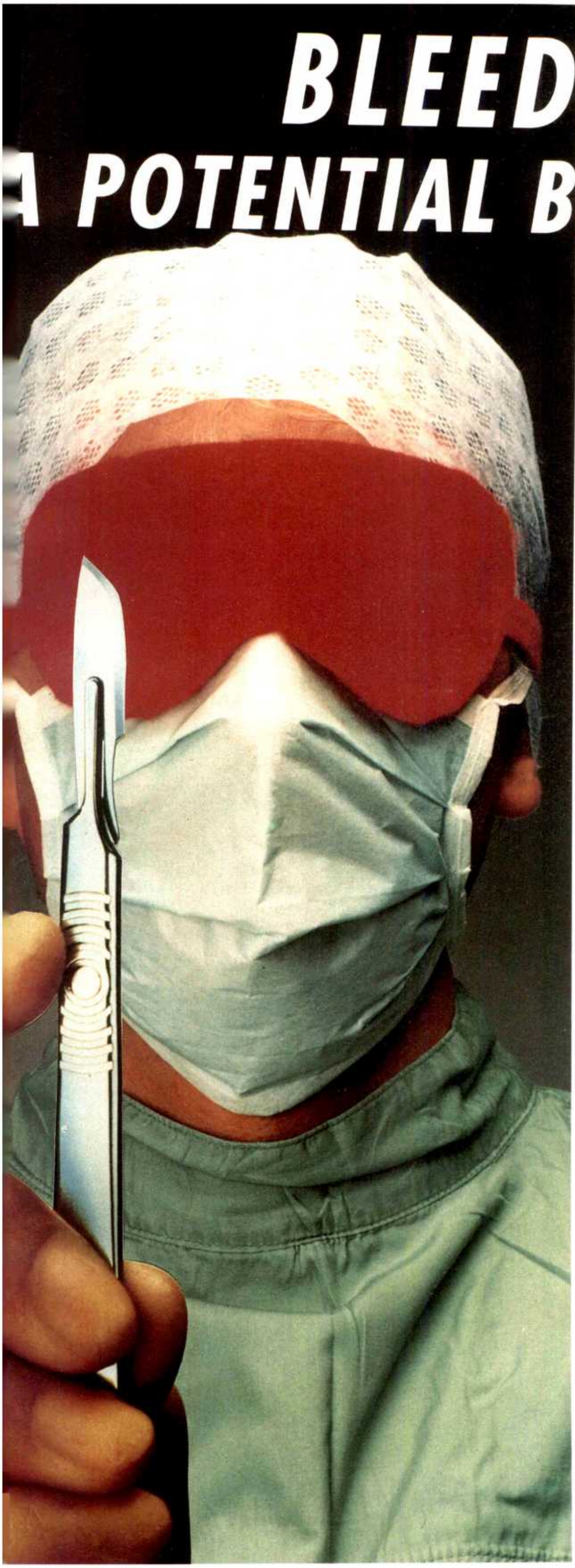
Interpretation

Statistical significance should not be confused with clinic significance. In particular, 'negative' findings should interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondar analyses, especially when they were suggested by an inspectio of the data.

NEW

BLEEDING,
A POTENTIAL BLINDFOLD



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References: **1.** Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. **2.** Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal p embolism and venous thrombosis by perioperative administration of subcutaneous heparin. New Engl J Med 1988; 318:1162-1173. **3.** Bergqvist D, Mätzsch T, Burmark U S et al. Low molecular weigh given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888-891. **4.** Eriksson B I, Kalebo P, Anthmyr B O et al. Prevention of D Thrombosis and Pulmonary Embolism After Total Hip Replacement. J Bone Joint Surg 1991;73A (4):484-493.

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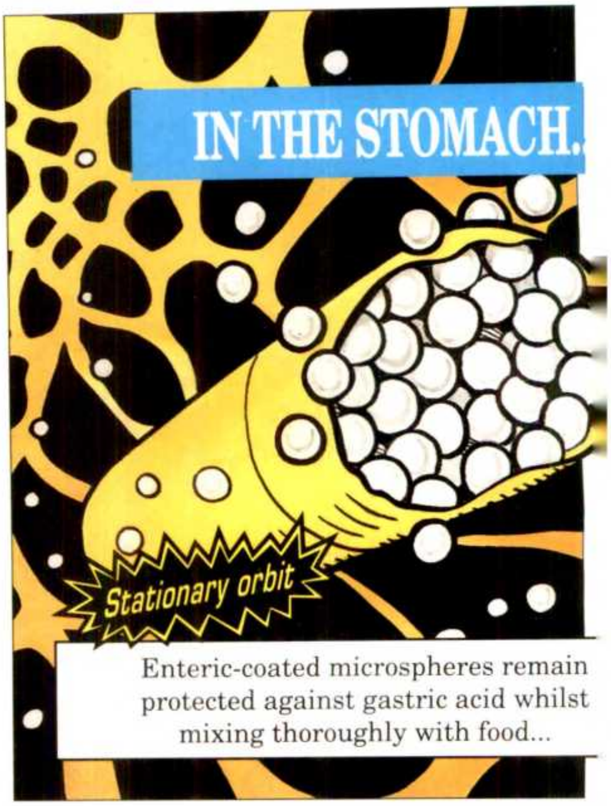

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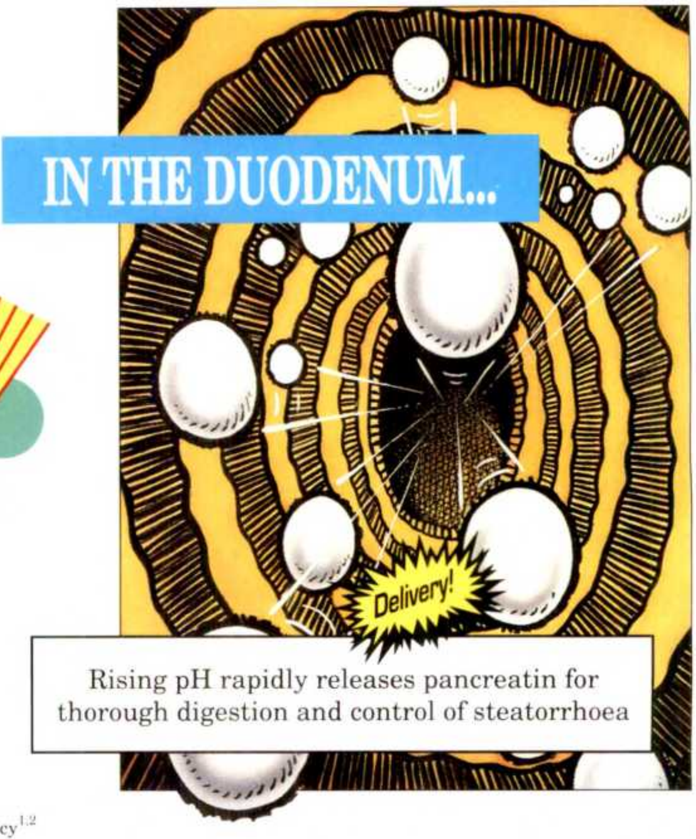
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References
1. Stead R J et al. *Thorax* 1987; **42**: 533-37
2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

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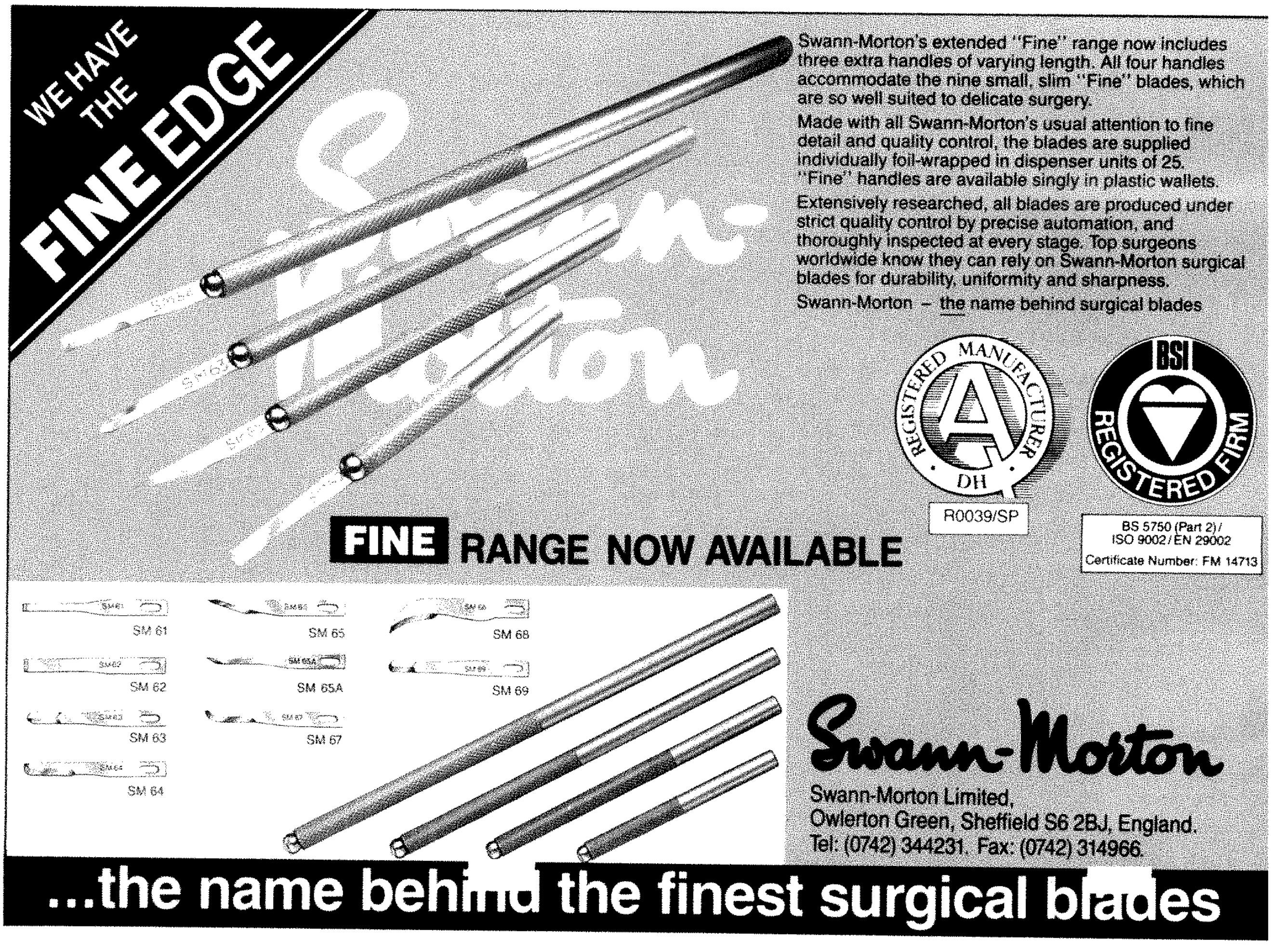

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Robin Williamson

Br. J. Surg. 1993, Vol. 80, August, 955–956

Oxygenation of the gut mucosa

The mechanisms regulating the supply of oxygen to the intestinal mucosa are complex. The oxygen consumption of this tissue is increased in critical illness such as sepsis, and gut ischaemia has been recognized as potentially harmful and an important factor in terms of outcome for the critically ill. The importance of these concepts is briefly discussed and a technology that allows monitoring of gut mucosal oxygenation in the clinical setting is described.

In some forms of shock there is a profound reduction in intestinal blood flow caused by severe vasoconstriction in the intestinal vascular bed. In other forms of shock, such as compensated haemorrhage, intestinal blood flow resistance might be increased to only a moderate degree. In still others, such as sepsis and uncompensated haemorrhagic shock, intestinal resistance to blood flow might be normal or decreased; changes in splanchnic organ blood flow then mainly parallel changes in cardiac output.

The distribution of blood flow within the intestinal wall has been studied during reduced arterial inflow pressure and during sepsis. During hypotension there is a significant redistribution of blood, favouring the mucosa and submucosa. Using a technique based on the rate of disappearance of instilled carbon monoxide from the intestinal lumen, the villous (absorptive site) blood flow has been studied. This was found to be maintained at normal levels even in cats that developed microscopically detectable injury of the mucosa following hypotension. Using the same technique it has been shown that absorptive site blood flow is not reduced even in intestinal segments that have sustained microscopic injury following standardized experimental sepsis[1]. Despite the finding of unchanged blood flow to the villi during shock, it has been demonstrated that local supply of small amounts of oxygen to the superficial mucosa through luminal perfusion during ischaemia caused by reduced blood supply or sepsis may prevent microscopic injury to the mucosa.

The vascular anatomy of the small intestinal mucosa provides the prerequisite for a counter-current exchanger, the existence of which is well supported theoretically and experimentally[2]. The physiological significance of the counter-current exchanger under normal conditions is uncertain, but there is no doubt about its significance under conditions of decreased perfusion. During hypotension the amount of blood flowing through the gut mucosa is maintained. However, more villi are perfused and the vascular cross-sectional area is, therefore, increased. Consequently, the mean transit time for blood flowing through the mucosa in hypotension is increased. When the transit time of intestinal mucosal blood flow is increased there is an increased efficacy of the counter-current exchanger and, as a consequence, the superficial part of the mucosa may be severely hypoxic despite an unchanged (or almost unchanged) supply of blood.

The small intestinal mucosa rapidly becomes injured during ischaemia. Following partial ischaemia, in which blood flow is reduced to one-quarter to one-third of normal (which is the expected blood flow during hypovolaemic shock), microscopic evidence of injury is found within 1–2 h. Increased capillary permeability, later followed by increased mucosal permeability, is detected before morphological signs of injury[3].

In addition to the damage caused by ischaemia, there is convincing evidence that intestinal injury also takes place during reperfusion[3]. This component of ischaemia–reperfusion injury is caused by increased generation of oxygen free radicals, in turn resulting from the activation of xanthine oxidase. Free radicals may damage tissue directly; they may also activate local polymorphonuclear neutrophils, which will then generate a variety of toxic agents, including proteases and more free radicals. As a consequence, endothelial injury occurs and there is microcirculatory disturbance.

During normal resting conditions, intestinal blood flow delivers more oxygen than is needed by the gut. Consequently, the portal vein has a high oxygen content. Intestinal blood flow can be reduced to about 50 per cent of the normal resting level for several hours without biochemical or morphological signs of injury. However, if blood flow is further reduced compensatory mechanisms can no longer provide enough oxygen for the needs of the tissue. The main compensatory mechanism is increased oxygen extraction; compensation therefore takes place at the expense of the amount of oxygen delivered to the liver[4].

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The intestinal oxygen requirement can be monitored clinically using a tonometric technique[5]. A saline-filled carbon dioxide-permeable balloon connected to an impermeable tube may be introduced into the lumen of a hollow viscus. After an appropriate time, the partial pressure of carbon dioxide (P_{CO_2}) of the saline inside the balloon will equilibrate with the P_{CO_2} of the gut lumen, which in turn is in equilibrium with the P_{CO_2} of the superficial intestinal mucosa. Knowing the arterial bicarbonate concentration, and assuming that it equals that of the mucosa, the mucosal pH (pH_i) may be calculated using the Henderson–Hasselbalch equation. The measurement of pH_i has been found to be largely independent of the acidity of the contents of the gastric lumen, and the technique has been validated in experiments in which the calculated pH_i was compared with the pH_i obtained by direct measurement[6]. It has been demonstrated, in moderate hypovolaemic and in septic shock, that the pH_i of the stomach, small intestine and colon correlate well[7]. The above technique has demonstrated that low gastric intramucosal pH is associated with increased mortality in critically ill medical and surgical patients in the intensive care unit. Furthermore, maintaining normal intestinal pH_i in the treatment of critically ill patients improves their chance of survival, provided pH_i was normal at admission[8].

During sepsis, splanchnic organ oxygen consumption is increased by up to 100 per cent[4]. This means that a delivery which provides enough oxygen for normal needs might not be adequate during sepsis. Furthermore, it has recently been demonstrated in an experimental model of porcine faecal peritonitis that early in the development of sepsis, when oxygen delivery is still in the normal range and consumption is significantly increased, intestinal mucosal pH is reduced, indicating anoxic metabolism[9]. Thus the increased oxygen consumption seen in sepsis may not be adequate to fulfil the needs of the tissue. Consequently, when monitoring patients with sepsis it is not enough to know only the intestinal blood flow – or even the delivery of oxygen to the gut. Moreover, monitoring of intestinal oxygen consumption is of limited value since one cannot know whether such measured consumption is adequate for the needs of the tissue.

Ischaemic intestine is likely to release toxic factors, including bacteria and bacterial endotoxin, through mural translocation[10]. The injured intestinal mucosa has been associated experimentally with the release of various toxins, including myocardial depressant factors[2]. Translocation of bacteria, which takes place to a certain degree in normal life, is much increased during endotoxaemia, sepsis and intestinal ischaemia. If the aim of monitoring critically ischaemic patients is to prevent anoxia of the intestinal mucosa and so minimize translocation, monitoring must be focused on oxygen consumption in relation to need. Therefore, monitoring of intramucosal pH should be an attractive proposition. It is suggested that monitoring gastrointestinal intramucosal pH, maintaining normal pH_i as a therapeutic goal, would improve survival in critically ill patients.

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Br. J. Surg. 1993, Vol. 80, August, 957–958

Operative cholangiography and laparoscopic bile duct exploration

The widespread adoption of laparoscopic cholecystectomy has reopened the debate on the role of operative cholangiography. During the era of open cholecystectomy, surgeons were divided into selective and routine users of operative cholangiography. Those advocating routine use pointed to the improved anatomical information the procedure could provide and argued that fewer duct injuries occurred as a result of its use. This notion gained support from several series reporting on bile duct injury which implicated the absence or poor quality of cholangiography as major aetiological factors in duct damage. In addition, the routine use of operative cholangiography has an impact on the training of surgeons that is generally accepted as beneficial. However, advocates of routine cholangiography have a harder case to prove when discussing choledocholithiasis. Several published series support the view that selective cholangiography in 'at-risk' patients (history of recent jaundice or pancreatitis, abnormal liver function test results, dilated common bile duct (CBD) on preoperative ultrasonography, large cystic duct, multiple small stones at cholecystectomy) is an acceptable alternative to routine cholangiography. Detractors of routine operative cholangiography highlight the impact of false-positive cholangiograms on small-calibre CBDs which, if explored, may later be prone to stricture formation.

The advent of laparoscopic cholecystectomy suited either selective cholangiography or a reliance on endoscopic retrograde cholangiopancreatography (ERCP) carried out before or after surgery to clear the CBD of stones. Laparoscopic cholangiography was not performed by many surgeons because of the increased operating time and the technical constraints of cystic duct cannulation, especially at a time when the operator was relatively inexperienced in the technique of laparoscopic cholecystectomy itself. It is interesting that the initial focus of surgical attention was more on retained stones than on definition of biliary anatomy. With the disquieting report from the Southern Surgeons Club, indicating a CBD injury rate in excess of 1 per cent and that the risk of duct injury was considerably greater during an operator's initial 13 or so cholecystectomies, emphasis shifted to the importance of biliary anatomical definition rather than retained stones[1]. Those who advocated cholangiography were soon encouraged by descriptions of successful laparoscopic cholangiography in the majority of patients in whom it was attempted.

The British Journal of Surgery and others have received many reports of easier, better and cheaper methods of performing laparoscopic cholangiography[2,3]. There is little to choose between these reports of various cholangiography catheters and anatomical approaches for performing the procedure. Whatever technique is adopted, proper visualization of the extrahepatic biliary tree facilitating safe dissection in Calot's triangle is of paramount importance if duct injury is to be avoided. It must be conceded, however, that radiological visualization alone of the extrahepatic biliary tree is insufficient protection against duct injury in the absence of careful dissection, especially during the learning phase of electrocautery or laser dissection.

Small stones in the CBD, discovered incidentally at cholecystectomy, are associated with an uncertain natural history and may pass spontaneously without harm[4]. This might suggest a policy of 'wait and see' or ERCP if symptoms occur after operation. However, the long-term effect of sphincterotomy in young people is uncertain. A tidier approach would be to deal with all the stone disease at one operation and so obviate any future uncertainty. The current feasibility of laparoscopic common duct exploration offers such a possibility. Such exploration, which is rapidly gaining favour with biliary surgeons experienced in laparoscopic techniques, perhaps affords the best of both worlds. Now the routine use of operative cholangiography, with its twin benefits of anatomical definition and delineation of filling defects within the CBD, may be married to the ability to explore the common duct and clear it of stones at a single operative sitting.

There are two approaches to the CBD, either direct or via the cystic duct. The transcystic approach involves dilatation of the cystic duct using graded dilators over a guidewire to a diameter capable of accommodating either an ultrathin flexible choledochoscope or ureteroscope[5,6]. A second camera may be fitted to the eyepiece of the endoscope, allowing visualization of the duct system on the monitor. The working channel of these endoscopes permits the introduction of a variety of

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instruments, such as basket extractors and balloon catheters, to achieve stone clearance; proximal duct visualization and stone clearance may not be possible. The direct approach allows access to the bile duct by enlarging the cystic duct opening or by a separate choledochotomy incision[7]; after this approach is used it is usual to introduce via one of the port sites a T tube, which is sutured into position laparoscopically. The relative merits of both techniques remain to be evaluated. Not all CBD stones or patients are suitable for such methods, and ERCP and sphincterotomy will remain the treatment of choice on occasion, most notably in the elderly and unfit.

Selective operative cholangiography at laparoscopic cholecystectomy with the 'safety-net' of endoscopic stone extraction may remain the preferred choice of many surgeons, although few would disagree that the ability to perform laparoscopic cholangiography is essential. Even so, operative cholangiography may yet acquire a prominent role in the expanding field of laparoscopic biliary surgery.

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Management of superficial femoral artery occlusive disease

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The prevalence of intermittent claudication in men aged 55–74 years is 4·5 per cent and a common cause of such claudication is superficial femoral artery (SFA) occlusive disease. The preferred management of patients with this condition remains a subject of discussion. Therapeutic options range from conservative treatment to endovascular intervention and surgical bypass or endarterectomy. Conservative therapy is the primary treatment of choice. However, if this fails and an endovascular technique is chosen, percutaneous transluminal angioplasty (PTA) is the best option; other endovascular methods have failed to achieve higher rates of technical success or patency. PTA should be considered only for short lesions (≤10 cm). The usual surgical option for SFA occlusive disease is femoropopliteal bypass using autogenous vein, which has an expected 5-year patency rate of 56–76 per cent. Patency rates decrease if other types of graft are used. An alternative to vein bypass is endarterectomy, with an expected 5-year patency rate of 35–71 per cent. A multicentre randomized trial should be conducted to determine the optimal management of claudication caused by SFA occlusive disease.

Much has been published about the treatment of superficial emoral artery (SFA) occlusive disease. If the clinical manifestation of this disease consists of limb-threatening schaemia there is usually no discussion as to whether treatment s necessary. However, the precise form of treatment remains undecided. Should an endovascular or surgical procedure be chosen, and should surgery consist of endarterectomy or emoropopliteal bypass? If the clinical manifestation is intermittent claudication, an additional question arises: should he patient be treated aggressively or should the disease be managed conservatively?

Prevalence

Peripheral vascular disease is one of the most common diseases in men. The 5-year incidence is 4 per cent for younger (35–44 years) and 18 per cent for older (55–64 years) age groups[1]. ntermittent claudication is often the first symptom of disease. The prevalence of claudication, determined in the Edinburgh study[2] of 1991, is 4·5 per cent in the 55–74 years age group, and that of major asymptomatic disease is 8 per cent. Only 30–50 per cent of patients with intermittent claudication are known to their general practitioner[3]. In 49–57 per cent of patients with intermittent claudication the responsible occlusive disease is located in the SFA[4].

Natural history

Intermittent claudication resulting from SFA occlusive disease is a relatively benign condition[5]. Over a period of 5 years a deterioration of symptoms is seen in only 25 per cent of patients[6]. Progression of atherosclerotic disease (seen in 50 per cent of patients[7] after a mean follow-up of 2·5 years) does not always result in a worsening of the symptoms. Progression of disease is influenced by the smoking habits of the patient and the presence of diabetes. Before the era of arterial reconstruction, amputation rates in patients with untreated intermittent claudication were between 3 and 10 per cent at 3–8 years' follow-up. In recent years these rates have improved to 2–6 per cent[8]. The requirement for arterial reconstruction because of disease progression ranges from 9 to 21 per cent per annum[4–6].

Besides the natural history of intermittent claudication, the life history of these patients must also be considered. Life history is strongly influenced by the high prevalence of coronary (19–90 per cent) and cerebrovascular (0·5–52 per cent) arterial disease[9], which results in a high mortality rate[10]. Boyd[11] stated that, of 100 patients aged 55–64 years treated with a bypass for intermittent claudication, only 72 per cent will be alive after 5 years; 16 per cent will be limited in lifestyle because of a non-fatal coronary or cerebral arterial episode and 12 per cent will have a further arterial thrombosis in either leg. Thus, only 44 of the 100 patients will benefit from vascular surgery; of these 44 patients, between 20 and 50 per cent will have had a graft failure during the 5-year period[11].

In view of the natural and life histories of patients with intermittent claudication, invasive treatment of SFA disease should be considered with reservation; the correction of atherosclerotic risk factors should be emphasized.

Conservative treatment

Exercise

As stated by Housley[12], conservative treatment of SFA occlusive disease resulting in intermittent claudication consists of five simple words: 'Stop smoking and keep walking'. In patients with stable intermittent claudication the treatment of choice is walking exercises. Exercise increases the walking distance by dilating the collateral vessels[13], altering local metabolic factors[14] and reducing blood viscosity[15]. An increase in walking distance is often seen without a rise in the ankle:brachial pressure index (ABPI).

A number of studies[16,17] have shown that, as a result of this treatment strategy, 40–78 per cent of patients may expect improvement or remain stable regarding their presenting complaint during a follow-up period of 2–6 years. The outcome of conservative treatment is influenced by the smoking habits of the patient[16]; smoking should be stopped. In a prospective randomized trial, Creasy *et al.*[18] compared the results of percutaneous transluminal angioplasty (PTA) and exercise in the treatment of intermittent claudication. In patients treated by PTA a significant rise in ABPI was seen without an increase

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in maximum walking distance, whereas those who received exercise training showed a significant rise in maximum walking distance without an increase in ABPI[18].

Medication

Intermittent claudication is a symptom of a disease (atherosclerosis) that cannot be cured. Conservative, endovascular or surgical treatment only establishes relief of symptoms or delays progression. Some studies claim a relief of symptoms or a delay of progression through medication.

One of the drugs that might cause a relief of symptoms is oxypentifylline (pentoxifylline). Oxypentifylline enhances red cell deformability by reducing hyperviscosity, decreasing fibrinogen levels and inhibiting platelet aggregation, which results in a decrease in blood viscosity and an increase in muscle tissue oxygenation. The result is an increase in walking distance[19]. In the placebo-controlled studies performed by Lee *et al.*[20] and Porter and colleagues[21] an increase in walking distance of 20 per cent was found. On the other hand, Green and McNamara[22] found that only 19 per cent of patients treated with oxypentifylline experienced an improvement of symptoms to the point where they did not feel limited in any way.

Progression of atherosclerosis can be delayed by the treatment of hyperlipoproteinaemia. In a randomized controlled trial by Duffield *et al.*[23], patients received cholestyramine, nicotinic acid or clofibrate, depending on their lipoprotein profile; a reduction in the progression rate of 60 per cent was achieved. Hess *et al.*[24] achieved a delay of progression by means of treatment with dipyridamole and aspirin. These drugs inhibit platelet function and reduce the progression of atherosclerosis[25]. Medication may reduce progression of atherosclerosis but it has a limited impact on the clinical manifestations of the disease. Only a minor improvement of walking distance can be achieved with medication.

Endovascular treatment

Percutaneous transluminal angioplasty

PTA was first described by Dotter and Judkins[26] in 1964. Over the years, the technique has been modified and is used to dilatate short stenotic lesions in the aortoiliac and femoropopliteal arterial segments, and for the recanalization and dilatation of short occlusive lesions of the femoropopliteal segment. Successful recanalization and dilatation, and long-term patency after PTA, depend on the length and nature of the lesion (stenosis or occlusion), extent of outflow disease, and site of the lesion (iliac or femoropopliteal segment)[27]. Capek *et al.*[28] found a significant difference in the success rate and cumulative patency rate between lesions >10 cm and those $\leqslant 10$ cm in length. The technical success rate of PTA varies in different series from 70 to 93 per cent. Overall cumulative 5-year patency rates[29] range from 43 to 73 per cent. The differences in these results arise partly from lack of standardization in the various studies, which makes comparison of the results difficult. Furthermore, some authors omit their initial technical failures of PTA in the final results and use modified criteria to define success[30]. Although PTA is a non-surgical procedure, the mortality rate is 1 per cent and a 1–4 per cent complication rate requiring surgical intervention has been described[27,31].

PTA is limited by the fact that recanalization of the occlusion is not always possible and by early recurrence of stenosis. Percutaneous transluminal laser angioplasty is claimed by some to overcome these limitations[32]. Using laser angioplasty, recanalization of long (>10 cm) occlusive lesions is possible. In a study by Pilger *et al.*[33], successful recanalization of SFA occlusions >3 cm was accomplished using the laser in 85 per cent of patients in whom PTA recanalization had failed[33]. On the other hand, Jeans and colleagues[34] found no difference in the recanalization rate between conventional PTA and the laser technique for short occlusions. In a number of studies the failure rate of laser angioplasty[35] varies from 15 to 30 per cent. The cumulative patency rate ranges from 49 per cent (3-year follow-up) to 53 per cent (5-year follow-up)[32,36]. No mortalit related to laser angioplasty has been described, but the technique has a considerable complication rate (14–32 per cent A number of these complications require surgical intervention[3] In view of these results, PTA remains the standard treatment and the additional value of the laser is still in doubt.

New endovascular techniques

Recently, new endovascular techniques have been developed such as catheter atherectomy, ultrasonic angioplasty and endoluminal stenting. A greater initial success rate is claimed for some of these techniques in recanalizing occlusions compared with PTA.

The atherectomy catheter combines a cutting and retrieval mechanism for atheroma, with a balloon similar to that used for PTA. The cutting mechanism removes atheroma protruding into an opening in the catheter shaft. After removal of the atheroma the balloon is expanded. Use of the atherectomy catheter allegedly reduces the risk of dissection, perforation and traumatization of the arterial wall compared with PTA[37] Percutaneous ultrasonic angioplasty uses ultrasound energy to recanalize the occluded artery. Recanalization can be accomplished without vasospasm, thrombosis, arterial dissection o intimal damage[38].

Endoluminal stents are placed in the artery and expanded at the location of a stenosis. These stents allegedly prevent restenosis. Because of the smooth wall of the stent, turbulence is diminished, which possibly reduces the chance of restenosis and occlusion[39]. In a comparative study, Do *et al.*[40] found tha stenting did not improve the primary patency rate of PTA in femoropopliteal occlusions. Up to the present, no studies giving the long-term results of these new endovascular techniques have been published, and so their value remains to be established.

Surgical treatment

Endarterectomy

Endarterectomy was first developed by Dos Santos[41] in 1947 and later modified by Vollmar[42]. In spite of promising results in early studies[43,44], endarterectomy was abandoned after several reports were published suggesting that it was inferior to femoropopliteal bypass grafting[45–47]. Since then, femoropopliteal bypass has been widely used and has largely replaced endarterectomy[48]. Recently, a few authors have favoured endarterectomy[49–51]. In a retrospective study[52] of 231 successfully performed endarterectomies, a 5-year overall cumulative patency rate of 71 per cent was achieved in this hospital, with a complication rate of 10 per cent and a mortality rate <1 per cent. Other studies have described similar results[49–51].

Endarterectomy has some specific advantages: the autologous saphenous vein is spared and so can be used for purposes other than ipsilateral femoropopliteal bypass, and no foreign-body is used, so minimizing the risk of infection. Furthermore, the collateral circulation is spared; this may be responsible for the fact that a great number of occlusions following endarterectomy do not need further treatment. In view of these advantages over femoropopliteal bypass, it is our opinion that endarterectomy is an important and useful alternative in the surgical treatment of SFA occlusive disease.

Femoropopliteal bypass

In 1949, Kunlin[53] performed the first femoropopliteal bypass for SFA occlusive disease using the autologous saphenous vein as a conduit. Since then a number of alternative conduits have been used: polytetrafluoroethylene (PTFE), human umbilical vein (HUV) and homologous denaturated saphenous vein[54–56]. Numerous studies have compared the results of different graft materials, but they seem to contradict one another. Some favour HUV over PTFE; others find no difference between the two[57–59]. Most authors consider the autologous saphenous vein as the best conduit[60], but others disagree[61,62]. Femoropopliteal bypass has traditionally been reserved for severe disabling claudication or limb-threatening ischaemia and carries a 57–72 per cent overall 5-year patency rate[63,64]. Patients with claudication and good distal run-off generally have better results[46,65], with a 5-year patency rate as high as 82 per cent and an operative mortality rate <3 per cent.

Discussion

The optimal method of treating SFA occlusive disease has not yet been established. No discussion is necessary about whether such occlusive disease resulting in limb-threatening ischaemia should be treated. However, with regard to the optimal treatment of intermittent claudication there is much controversy and the literature is unable to provide the answer. *Table 1* shows the patency rates of the surgical procedures and *Table 2* those of endovascular techniques. Results of various studies differ for the same technique and there have been few prospective randomized studies comparing the different treatments. Those that have been performed differ in their conclusions; Lundgren *et al.*[76] favoured surgical reconstruction (in combination with physical exercise), whereas Creasy and colleagues[18] suggested exercise alone.

In our opinion, the first step in the treatment of intermittent claudication is contained in the recommendation of Housley[12]: 'Stop smoking and keep walking'. Physical exercise will lead to an improvement or stabilization of symptoms in 40–78 per cent of patients. Furthermore, the general condition of the patient will also be improved by exercise. If symptoms continue to affect quality of life significantly, the next step is to answer the question: Will the outcome of intervention be limited by concomitant disease? If the answer is 'no', intervention should be considered. Studies by Wilson *et al.*[4] and Imperato and co-workers[5] have shown that 20 per cent of patients with stable claudication will have a surgical intervention for this or a related symptom within a period of 2·5 years. Should treatment[77] consist of an endovascular procedure, surgery or a combination of both? If surgery is chosen, should it be endarterectomy or femoropopliteal bypass?

In our opinion, interventional options for short-lesion (≤10 cm) SFA occlusive disease are endovascular techniques or endarterectomy. If an endovascular procedure is chosen, the best option is PTA. Other endovascular techniques do not appear to provide any advantage over PTA and, in particular, laser angioplasty does not achieve a better recanalization rate than PTA[34], especially since the development of new guidewires for the latter. Atherectomy has a high incidence of restenosis[72] and stenting has not yet been proven to increase patency rates[39,40]. PTA is the first choice and patency rates vary between 53 and 82 per cent after 2-years' follow-up. This might be improved by use of monitoring methods during the procedure, such as techniques using intravascular ultrasonography. If such methods detect residual stenosis, atherectomy or stent placement could be performed.

In our opinion, endarterectomy is the best surgical option for short lesions. It is relatively safe, with a 5-year overall cumulative patency rate[52] of 71 per cent, and if it fails autologous saphenous vein bypass remains possible.

For long (>10 cm) lesions of the SFA the interventional options are PTA, femoropopliteal bypass or endarterectomy. Studies by Zeitler *et al.*[73] and Capek and colleagues[28] have shown that the failure rate of PTA increases dramatically if lesions >10 cm are treated; PTA should not be used in such

Table 1 *Patency rates of surgical procedures*

				Cumulative patency rate (%)							
				Length of follow-up (years)							
Reference	Year	Intermittent claudication (%)	No. of procedures	1	2	3	4	5	6	7	8
Endarterectomy											
Kouchoukos *et al.*[66]	1967	49	120	58	50	43	35	35	—	—	—
Darling and Linton[46]	1972	62	87	69	55	45	38	36	33	29	23
Inahara and Scott[49]	1981	85	105	95	89	80	75	70	61	58	55
Ouriel *et al.*[50]	1986	61	94	75	—	66	—	—	—	57	—
Vercellio *et al.*[51]	1986	73	160	81	—	—	—	64	—	—	59
van der Heijden *et al.*[52]	1992	80	231	85	80	78	75	71	65	60	55
Autologous saphenous vein grafts											
Darling and Linton[46]	1972	57	345	88	82	79	74	72	68	67	62
Veith *et al.*[60]	1986	18	85	—	—	—	61	—	—	—	—
Kent *et al.*[67]	1988	100	87	—	—	—	—	72	—	—	—
Blankensteijn and van Vroonhoven[68]	1988	100	109	86	—	81	—	—	—	—	—
Taylor *et al.*[64]	1990	20	76	87	—	77	77	76	—	—	—
McCollum *et al.*[58]	1991	—	217	—	—	62	—	—	—	—	—
Johnson[59]	1993	41	226	79	73	65	59	56	—	—	—
Polytetrafluoroethylene grafts											
Veith *et al.*[60]	1986	11	91	—	—	—	38	—	—	—	—
Blankensteijn and van Vroonhoven[68]	1988	100	101	81	—	59	—	—	—	—	—
Kent *et al.*[67]	1988	100	63	—	—	—	—	55	—	—	—
Whittemore *et al.*[69]	1989	28	182	—	—	—	—	42	—	—	—
McCollum *et al.*[58]	1991	68	104	61	56	48	—	—	—	—	—
Aalders and van Vroonhoven[70]	1992	41	49	67	—	—	—	39	—	—	—
Quinones-Baldrich *et al.*[71]	1992	50	219	—	—	—	—	61	—	—	53
Johnson[59]	1993	27	266	76	72	62	42	39	—	—	—
Human umbilical vein grafts											
Blankensteijn and van Vroonhoven[68]	1988	100	41	84	—	84	—	—	—	—	—
Dardik *et al.*[72]	1988	—	96	84	82	77	72	71	62	—	—
McCollum *et al.*[58]	1991	73	87	68	63	57	—	—	—	—	—
Aalders and van Vroonhoven[70]	1992	36	47	90	—	—	—	71	—	—	—
Johnson[59]	1993	31	260	80	74	70	69	60	—	—	—
Homologous vein grafts											
van Reedt Dortland *et al.*[56]	1991	41	66	82	78	76	76	76	—	—	—

Table 2 *Patency rates of endovascular procedures*

Reference	Year	Intermittent claudication (%)	No. of procedures	Initial failure rate (%)	Cumulative patency rate (%) Length of follow-up (years) 1	2	3	4
Percutaneous transluminal angioplasty								
Zeitler *et al.*[73] (≤12 cm)	1989	100	273	10	—	82	—	—
Zeitler *et al.*[73] (>12 cm)	1989	100	82	33	—	60	—	—
Capek *et al.*[28]	1991	74	152	10	73	55	46	—
Johnston[74]	1992	80	254	4	63	53	51	44
Vroegindeweij *et al.*[75]	1992	100	14	8	61	—	—	—
Percutaneous transluminal laser angioplasty								
Sanborn *et al.*[35]	1988	66	129	23	56	—	—	—
Perler *et al.*[32]	1989	78	47	30	29	—	—	—
Lammer *et al.*[36]	1991	67	338	15	62	55	48	—
Percutaneous transluminal atherectomy								
Vroegindeweij *et al.*[75]	1992	100	16	0	25	—	—	—

cases. The patency rates achieved with endarterectomy and femoropopliteal bypass are comparable. The specific advantages of endarterectomy have already been discussed.

To reach a consensus about whether an endovascular procedure is preferable to endarterectomy for short stenotic lesions or occlusions, or whether endarterectomy is preferable to femoropopliteal bypass for long stenotic lesions or occlusions, a multicentre prospective randomized trial should be conducted[78]. Although the patency rate after endarterectomy is considerably better than that after PTA (*Tables 1* and *2*), PTA is a non-surgical technique with a relatively low morbidity rate. Furthermore, patients need only a short hospital stay. For these reasons, comparison of PTA and endarterectomy is justified. Only in this way will we finally answer the question: What is the preferred management of SFA occlusive disease?

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Surgical evaluation at the crossroads

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Surgeons have lagged behind physicians and oncologists in embracing randomized controlled clinical trials. This paper suggests that a complete, accurate and objective comparison of the outcome of a novel intervention with that of a traditional intervention in previous years, or in another surgical group, can yield valuable information and can lead surgeons to improve their practice. There has recently been a decline in the number of randomized controlled trials published in The British Journal of Surgery*; this may reflect the unwillingness of many patients to allow their surgical treatment to be decided by chance.*

No one is foolish enough, or blind enough, to ignore the enormous importance of randomized controlled clinical trials in eliminating as far as possible the biases inherent in anecdotal accounts of medical practice: they remain the 'gold standard' for clinical research. Thousands of patients have been helped by trials, particularly of various drug regimens in oncology and cardiology, and meta-analyses permit deductions about the need for further trials to be made at any given level of confidence[1].

It has become increasingly more difficult, however, for surgeons to reconcile respect for patients' autonomy with the requirement that they should allocate individuals to receive treatment at random. Patients are better informed than they were 30 years ago and most people expect to share in decision making about their treatment. They ask: 'What are the choices? Which do you advise? And why?' In the end they will want to follow their own preference after being advised by the surgeon, and will not want to allow the decision to be left to chance. Many surgeons are coming round to the view that important clinical decisions can now be made only with the full cooperation and consent of the patient, and that means without recourse to randomization[2].

Some aspects of the controlled trial and its alternatives are discussed below in the light of these developments.

Problems with randomized controlled trials

What is acceptable as 'proof'?

One of the prerequisites for a randomized controlled trial is that both doctor and patient shall be ignorant about the relative superiority of the regimens being tested. It is morally wrong for a doctor to allocate a patient to a regimen that he or she rightly or wrongly thinks or believes is inferior. Any preconception should be based on adequate scientific or experiential grounds rather than prejudice or dogma; some say that this rarely happens, and so justifies the search for an objective comparison by undertaking randomized controlled trials.

As the trial progresses, however, events may upset the assumed equivalence of the regimens. A good example is the treatment by extracorporeal membrane oxygenation of neonates with persistent pulmonary hypertension[3]. Of the first 19 infants enrolled, four of the ten randomized to receive conventional treatment died, compared with none of the nine assigned to extracorporeal membrane oxygenation. Although this outcome was not statistically significant ($P = 0{\cdot}09$, Fisher's exact test), the trial – which by its nature could not be 'blind' – was stopped. Clinicians found themselves ethically unable to wait for the evidence which might have indicated that chance alone had led to the observed results.

Rules about when a trial should be stopped

The decision about when to stop a trial has been controversial since the first properly randomized trial[4] in 1947. Pocock recognized the conflict between duty to the individual and duty to the community (individual against collective ethics), as well as the requirement that a patient should not be assigned to a treatment that is considered inferior when the trial starts, or seems to emerge as such as the trial progresses. He insisted that more stringent statistical rules about the acceptable level of significance of observed differences should be adopted for interim analyses. He did not, however, consider the influence of confidence intervals.

The difficulty with such rules is that they are fine in theory but difficult to put into practice. If the clinicians who are entering patients into a trial become aware that substantial differences between treatment regimens are emerging, whether or not they attain the levels of significance originally agreed they will not be able to sustain their indifference to the respective merits of the arms of the trial. The only ethical way in which interim analyses can be acceptable is for both professionals and patients to agree the statistical bounds for stopping, as in the example of the West of Scotland Coronary Prevention Trial quoted by Pocock[5]. Analyses should be made by someone who does not communicate the results to the participants unless the agreed bounds are reached or there is evidence of harm to patients.

Delay in application of results

Ignorance. The acceptance of a new treatment may be delayed, so that patients continue to be entered into randomized controlled trials and those in the control arm continue to receive inferior treatment. A cumulative meta-analysis of thrombolytic treatment for acute myocardial infarction concluded[6] that it could have been adopted in 1973 after only eight trials. The results of the next 25 trials, which enrolled an additional 34 542 patients, added nothing to the odds ratio that established efficacy, but merely narrowed the confidence interval. This information was gained in retrospect and after the technique of meta-analysis had become highly developed. Although the lesson is clear – satisfactory analysis of the available data from randomized controlled trials is essential to avoid their unnecessary continuance or repetition – how to implement it is not. How can one make people believe the results of even the best conducted trial? Who is to proclaim: 'Now we must change our practice'? And when?

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In addition, randomized controlled trials deal with the efficacy of a treatment only in a defined, usually self-selected, roup of patients and the results do not necessarily mean that the treatment will be effective for every patient with that disease.

The General Accounting Office in the USA has proposed a ew strategy for research into the effectiveness of treatment, which is called 'cross-design synthesis'[7]. This combines the results of randomized trials with findings from analyses of databases of patients' records. As an editorial[7] in *The Lancet* ndicated:

> '... the difficulties of applying the results of meta-analyses of randomised controlled trials to individual patients remain'.

Perhaps the development of audit in clinical research will help.

Biological and technical. Delay may also occur because of the time taken to evaluate some results, particularly for the treatment of malignant disease. During the long lag period a rial may be overtaken by a conceptual advance in management. Low anterior resection for carcinoma of the middle third of the ectum is a case in point. The conventional view was that abdominoperineal resection was essential for adequate clearance of the tumour. Controlled trials were launched to test this, but surgeons and patients 'voted' for anterior resection because of the surgical challenge and the improved quality of life long before there was adequate hard evidence to do so. The idea hat decisions to change practice must be made only after digesting the results of a randomized controlled trial may be cientifically commendable, but it does not allow for the human endency to want to try new ways that seem to be improvements; nor does it take into account the human capacity for elf-deception.

Laparoscopic cholecystectomy has been another technical change that has led to outcomes which, in some people's eyes, preclude a clinical trial, and the adoption of other laparoscopic procedures without formal justification by a randomized controlled trial may well be repeated.

Modifying the approach to randomization

Nowadays most patients want to be consulted at all stages of their investigation and treatment, whether or not surgery is one of the options. Randomization without the patient's cooperation is therefore explicitly wrong. As Dudley[8] has commented:

> 'Patients often wish for a personal decision by their medical adviser rather than for an invitation to be spun on a roulette wheel'.

The doctor–patient relationship may well be damaged by admission of uncertainty, and some authorities[9] are convinced that a measure of authoritarianism, paternalism and dominance is essential to good medical care. These traits are not compatible with randomization.

Zelen[10] tried to get round some of the difficulties of uninformed randomization; he suggested that patients should be randomized to receive 'control' or 'experimental' treatment before they were asked for consent. Only those allocated to the experimental group would be told that they were taking part in a trial. This approach can be faulted because it conceals information from the patients in the control arm and restricts their choice. Zelen later extended his idea in the context of breast cancer to a 'double randomization consent design'[11]: eligible patients are randomized to receive treatment A or B and are then asked whether or not they wish to have the selected treatment.

There are many other variations on straightforward randomization based on the reproduction of random events, such as the toss of an unbiased coin or appropriately generated numbers from mathematical formulae. It has been suggested, for example, that half the patients (chosen at random) should be allocated to a physician or surgeon who practises one treatment and the other half to one who practises the other[12]. Alternatively, patients can be allocated by 'play the winner' randomization: if one treatment is successful the next patient is put into that arm. This means that the results of a trial must be audited continuously (possibly by an independent body) and it is inapplicable to trials in which the outcome is apparent only after a lapse of time. As far as the author is aware, neither 'play the winner' randomization nor Zelen's ideas have been widely accepted.

None of these ways of deciding treatment takes account of the need to consider tailoring that treatment to the individual patient, to consider social and other factors, and to give an opinion based on fact within the surgeon's limits of knowledge and experience.

If the need to inform patients about randomization is accepted, it is likely many will refuse to go on the 'roulette wheel' and will therefore receive the same treatment as the controls. To discover whether this introduces bias by selecting a group that may have different characteristics from the control or treatment arms, it is necessary that outcomes of all potential and actual subjects be analysed and reported[13]. The St Mary's Hospital Large Bowel Cancer Project[14] studied prospectively the outcome of 4572 consecutive patients who underwent operation for colorectal cancer between 1976 and 1980 in 23 hospitals in the UK. During this audit, surgeons at 11 of the hospitals took part in a randomized controlled clinical trial of the influence on survival of continuous postoperative intraportal infusion of heparin, or of 5-fluorouracil (5-FU) plus heparin, or of no infusion[15]. By design or oversight 202 eligible patients were not randomized and received no adjuvant treatment. Of those who were randomized, there were 145 in the control group, 123 in the heparin group and 130 in the 5-FU group. The overall survival rates were similar in all groups, but patients with lymph node metastases who received 5-FU plus heparin had a significant survival advantage (16 per cent) over those in the other groups.

The important aspect of this publication is that the fate of the patients who were eligible but not randomized was reported; it did not differ significantly from that of the randomized control group, which suggests that bias had not been introduced by their omission. Exclusion as a consequence of patient choice will reduce the rate of accretion to a trial, perhaps to a level that makes its prosecution impractical, but this is a hazard that must be faced.

A retreat from randomized trials?

The starting point of any randomized controlled trial is the null hypothesis: the investigator thinks that there is no difference between two types of treatment and sets up a trial to attempt to disprove this. Although in a limited way impeccable, this approach runs against the grain of the medical mind, which tries something new on the assumption that it is an improvement. Such a premise may be at best unsound and at worst wrong, and the debris of therapeutic disasters that has accumulated over the years is often quoted as the best justification for randomized controlled trials. New treatments are not, however, introduced before a lot of hard thinking has been done about the mechanisms of particular diseases and the rationality of certain approaches. The adoption of the null hypothesis at an early stage may discourage rigorous theoretical analysis of the possible benefits of a different course of action[16]. Many answers to clinical questions can be obtained from a complete and careful study of the outcome of treatment in a consecutive series of patients; this is one aspect of audit[14].

Introduction of new procedures

In pharmacological work it has been recommended[17] that an open study of a consecutive series should not precede a randomized controlled trial because the results of the open trial could bias investigators regarding the new treatment. By contrast, when a new operation is undertaken there is likely to be more of a technical 'learning curve' than for a less

Table 1 *Research papers in* The British Journal of Surgery, *1965–1992*

	1965	1975	1985	1992
Randomized controlled trials	0	14	28	12
Clinical audit studies	73	111	140	157
Animal studies	23	13	22	24
Laboratory studies	1	8	16	57

interventional form of treatment, and the results of the first few operations may differ from those obtained later. It is important, therefore, that surgeons should undergo a period of training before starting the assessment of any new operation, and then be given the opportunity to decide whether or not a randomized controlled trial can still be regarded as ethical[18]. For example, concerning laparoscopic cholecystectomy, it has been stated[19]:

> 'After weighing the pros and cons for the timing of a randomized controlled trial of 'conventional *versus* laparoscopic cholecystectomy' we were in favour of not starting such a trial from the very beginning. Instead, consensus was obtained first to initiate a careful observational study of the new procedure in parallel with a study of conventional cholecystectomy ... [after the first 100 laparoscopic cholecystectomies] ... Accepting the ethical principle of autonomy means that randomized controlled trials have become obsolete for alternative treatments that are of concern to the patients.'

A randomized controlled trial of laparoscopic and minicholecystectomy in Montreal, Canada, was stopped after 70 patients had been entered because 'patient recruitment had become difficult'[20]. Significant differences in favour of the laparoscopic technique were found in the duration of hospital stay, duration of convalescence and amount of pain after operation. There are, however, several groups undertaking randomized controlled trials of laparoscopic cholecystectomy compared with either minicholecystectomy or open cholecystectomy, and it will be interesting to see what effect their results have on the use of the technique.

It was experience and not randomized controlled trials that established the place of balloon-catheter dilatation of cardiac valvular stenosis in young people with cusps that are fused but not heavily calcified[21]. Only an ethics committee unaware of the published outcome would sanction a randomized trial between balloon dilatation and valve replacement.

It is to be hoped that we have moved forward from the era when, in spite of good non-randomized studies, the unswerving diktat was that a randomized controlled trial was imperative. To assess whether this is the case, all the papers published in *The British Journal of Surgery* for the years 1965, 1975, 1985 and 1992, excluding reviews, editorials, case reports, abstracts and brief mentions of new techniques, have been compared (*Table 1*). Clearly, this approach is somewhat arbitrary; it may reflect merely changes in editorial policy. The number of randomized controlled trials that were reported peaked in 1985, but in none of the years did their number approach those of reports that came under the heading 'clinical audit'. Indeed, the number of the latter has increased progressively since 1965. It seems, therefore, that 'assessment without randomization' is not merely a reflection of editorial policy, but the result of a general drift of opinion away from the idea that randomized controlled trials are the only way in which success or failure should be judged. What a journal publishes is, after all, only a reflection of the best work that is submitted.

What can be learned?

There appear to be few questions in surgical clinical research that should now be answered by randomized controlled trials, despite the debt that is owed to the technique. Too much scientific effort has been and is directed at ridiculing other usef methods of obtaining information. Important advances wi increasingly depend on complete, accurate and objecti reporting of the outcome of consecutive series based o apparently logical scientific foundations. Data must be collecte prospectively in relation to the hypothesis entertained.

If some form of controlled comparison is possible c necessary, be it historical or contemporary (the results another surgeon, or at another hospital), it must be teste against a similar series or the idea of comparison rejected. Bia occurs when there are risk factors of which the researcher i unaware, but this can happen in randomized controlled trial as well as in audit of consecutive patients. The most importan step in the avoidance of bias is continual awareness of it existence.

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Venous assessment using air plethysmography: a comparison with clinical examination, ambulatory venous pressure measurement and duplex scanning

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Air plethysmography was compared with clinical assessment, ambulatory venous pressure measurement and duplex ultrasonography in 103 unselected limbs with venous disease and ten normal control limbs without such disease. Measurements of venous function obtained by air plethysmography showed considerable overlap between groups of limbs classified on the basis of clinical condition or by the presence of popliteal incompetence detected by duplex scanning. The measurement of venous refilling time using air plethysmography correlated poorly with that obtained by venous cannulation ($r_S = 0{\cdot}58$). The residual volume fraction did not correlate with ambulatory venous pressure measurement ($r_S = 0{\cdot}04$). Air plethysmography was not found to be as useful as previously reported. The residual volume fraction should not be accepted as a substitute for ambulatory venous pressure measurement, which remains the 'gold standard' test of venous function.

Ambulatory venous pressure (AVP) measurement has been used since the 1940s to assess venous disorders and is accepted as the 'gold standard' test of venous function. The test is however invasive; it requires cannulation of a pedal vein and investigators have long sought a non-invasive method that is equally reliable in assessing venous disorders. Air plethysmography has recently been reintroduced using a novel design of plethysmograph that is portable and simple to use. The technique is claimed to quantify venous insufficiency and its results said to correlate well with those from AVP measurement. This study compared air plethysmography with clinical examination, AVP measurement and duplex ultrasonography.

Patients and methods

A total of 103 limbs of 55 patients attending a vascular clinic were studied. All patients had been referred with varicose veins or chronic venous insufficiency. Fourteen limbs had previously been shown to have deep vein thrombosis (DVT) on venography. In addition, a control group of ten limbs in ten subjects without varicose veins and with no family history of varicose veins was studied. Limbs with coexisting arterial disease were excluded.

Each patient was assessed clinically by one author (S.P.K.P.) to divide limbs into three groups:

1. Normal controls. These patients had no history of varicose veins, venous insufficiency or DVT. In addition they had no family history of varicose veins ($n = 10$).
2. Limbs with varicose veins but no ulceration. These limbs had varicose veins with or without skin changes but no history of ulceration ($n = 66$).
3. Limbs with active or healed venous ulcers; those that had remained healed as a result of previous venous surgery were excluded ($n = 37$).

Measurements of air plethysmography, AVP and duplex scanning were carried out on the same day for each limb.

The technique of air plethysmography has been described previously[1]. Briefly, the device comprises a 35-cm long polyvinyl chloride air chamber that surrounds the lower leg and is connected to a pressure transducer and chart recorder. After inflation and a period of equilibration at room temperature (22–24°C), the device was calibrated by recording pressure changes as 100 cm^3 air was injected and then removed. This calibration was repeated five times on 22 occasions to measure the coefficient of variation on repeated inflation and deflation. In addition, the calibration was performed both before and after the clinical measurements on 11 occasions to measure the drift during the procedure.

The following volume changes were assessed by reading from the pressure recorder. The leg was elevated to empty the veins as much as possible; the subject then stood erect with weight on the opposite limb until the veins were full. This volume change represented the functional venous volume and the time taken to fill 90 per cent of venous volume the 90 per cent venous filling time (VFT_{90}). The venous filling index (VFI) was derived from:

$$\mathrm{VFI} = 90\% \times \text{venous volume}/\mathrm{VFT}_{90}$$

Each subject then performed one heel-raise manoeuvre and the volume displaced during this manoeuvre was recorded as the ejection volume; the ejection fraction was calculated as the ejection volume divided by the venous volume. Ten heel-raise manoeuvres were then performed to reach a residual volume plateau; the residual volume fraction (RVF) was then residual volume/venous volume.

AVP recording has also been previously described[2]. The technique involves cannulating a pedal vein with a 21-Fr cannula connected to a pressure transducer and chart recorder. Subjects stood erect to record the resting pressure. Ten heel-raise manoeuvres were then performed at the rate of 1 s^{-1} to reach an AVP plateau. The time taken for the pressure to return to 90 per cent of the resting value was recorded as the 90 per cent refilling time (RT_{90}). The normal control group was not subjected to AVP assessment.

Duplex ultrasonography was performed using a scanner with an 8·5-MHz probe and pulsed Doppler signal (Hitachi, Bedford, UK). Subjects sat on the edge of a couch with legs dependent and relaxed; a foam wedge was used as a back rest to help them relax. Each subject performed the best Valsalva manoeuvre they could manage. If this failed to produce retrograde flow in the vein being interrogated, calf compression was applied and then released. If either manoeuvre produced reflux of duration $>0{\cdot}5$ s the vein was classified as incompetent[3]. All major veins in the leg were examined in the control group. In patients with venous disease the popliteal vein alone was assessed to classify limbs into those with and without deep venous incompetence at this level.

Results

The coefficient of variation on repeated inflation–deflation was 5·8 per cent and the calibration drift during the procedure 0·54 per cent.

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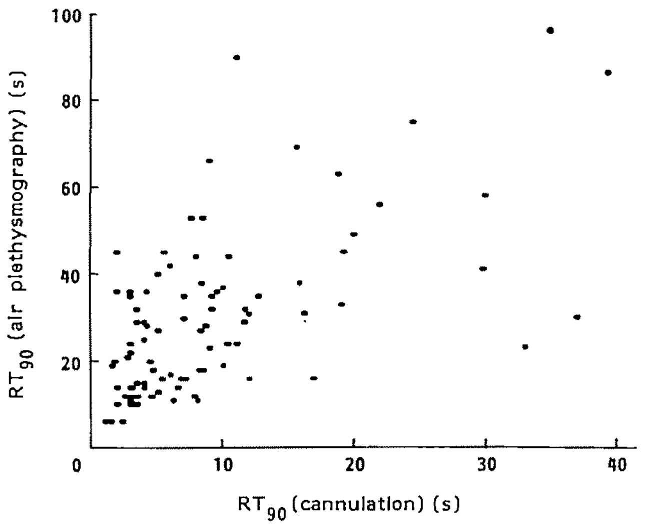

Figure 1 *The 90 per cent refilling time* (RT_{90}) *measured by air plethysmography* versus *that derived from venous cannulation.* $r_s = 0{\cdot}58$

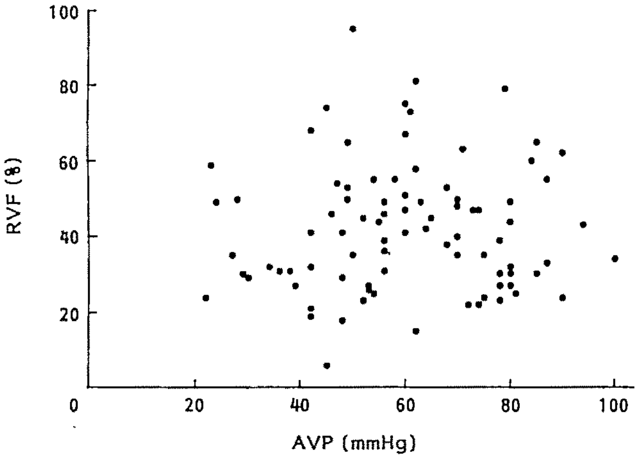

Figure 2 *Residual volume fraction* (*RVF*) versus *ambulatory venous pressure* (*AVP*). $r_s = 0{\cdot}04$

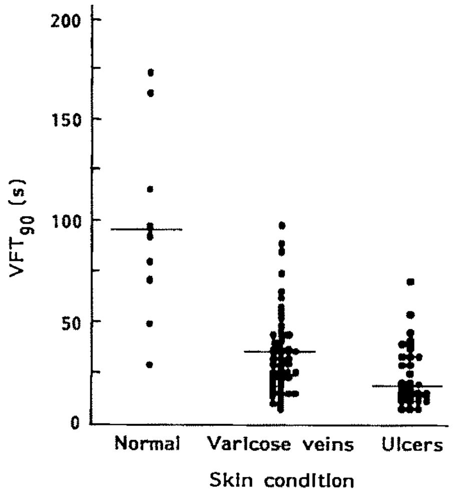

Figure 3 *The 90 per cent venous filling time* (VFT_{90}) versus *skin condition in ten control limbs, 66 limbs with varicose veins without ulceration, and 37 limbs with active or healed ulcers. Bars are medians*

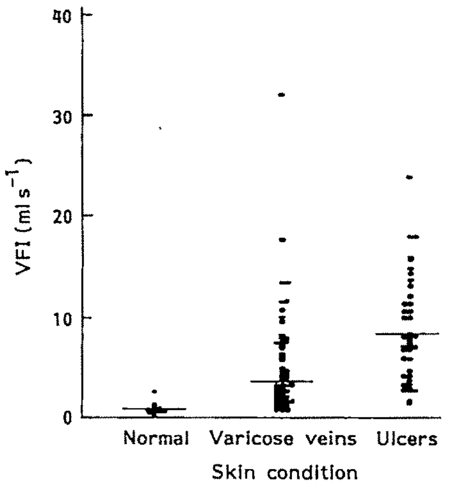

Figure 4 *Venous filling index* (*VFI*) *in ten control limbs, 66 limbs with varicose veins without ulceration, and 37 limbs with active or healed ulcers. Bars are medians*

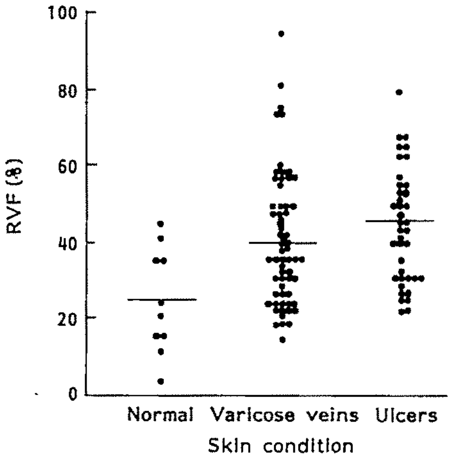

Figure 5 *Residual volume fraction* (*RVF*) *in ten control limbs, 66 limbs with varicose veins without ulceration, and 37 limbs with active or healed ulcers. Bars are medians*

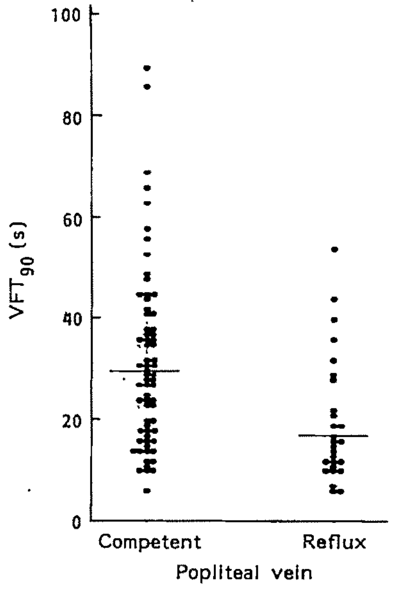

Figure 6 *The 90 per cent venous filling time* (VFT_{90}) *in 73 limbs with competent popliteal segments and 30 limbs with popliteal reflux. Bars are medians*

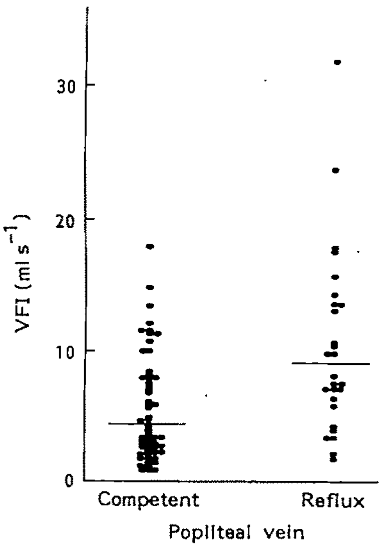

Figure 7 *Venous filling index (VFI) in 73 limbs with competent popliteal segments and 30 limbs with popliteal reflux. Bars are medians*

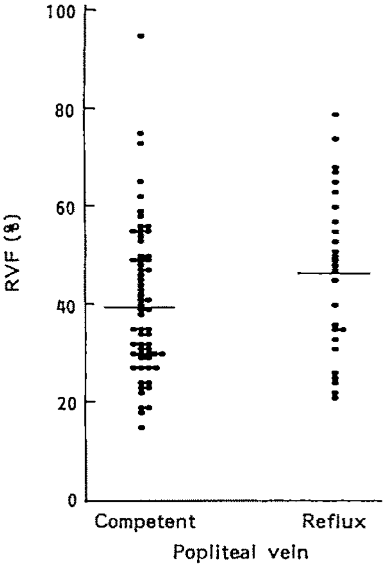

Figure 8 *Residual volume fraction (RVF) in 73 limbs with competent popliteal segments and 30 limbs with popliteal reflux. Bars are medians*

Air plethysmography and ambulatory venous pressure measurement

The two measurements of RT_{90} and AVP by venous cannulation were compared with their counterparts VFT_{90} and RVF as measured by air plethysmography. *Figures 1* and *2* demonstrate a poor correlation between RT_{90} and VFT_{90} ($r_S = 0{\cdot}58$), and between AVP and RVF ($r_S = 0{\cdot}04$).

Air plethysmography and clinical examination

There was evidence of active or healed ulceration in 37 limbs; 66 had no ulceration. The median VFT_{90} was 95·5 s in control limbs, 30·5 s in those with varicose veins and 21·0 s in those with ulcers (*Figure 3*). The median VFI in these three groups was 0·85, 3·7 and 8·5 ml s^{-1} respectively (*Figure 4*). Corresponding values for the median RVF were 25·5, 39·5 and 44·0 per cent (*Figure 5*).

Air plethysmography and duplex scanning

All limbs examined had a patent popliteal vein; 30 had popliteal reflux and the remainder a competent popliteal vein. The control group had no evidence of venous insufficiency on duplex scanning. The median VFT_{90} in limbs with popliteal reflux detected on duplex scanning was 17·0 s, compared with 29·5 s in those without such reflux (*Figure 6*). The median VFI in limbs with popliteal reflux was 9·0 ml s^{-1} compared with 4·4 ml s^{-1} in those without (*Figure 7*). The ejection fraction was measured in 30 limbs with popliteal reflux. The median ejection fraction in 15 limbs with venous ulceration was 47·0 per cent, compared with 50·5 per cent in 15 without.

The median RVF in limbs with popliteal reflux was 46·5 per cent compared with 39·5 per cent in those with a competent popliteal vein (*Figure 8*).

Discussion

All measurements using air plethysmography in this study show a wide scatter of data, with overlap between the different groups. There is a trend in the data, however, towards a higher VFI and shorter VFT_{90} in more severely affected limbs as determined by clinical examination. Increased venous reflux, as measured by VFI, is associated with an increase in the clinical severity of venous disease (normal, varicose or ulcerated). In addition, the presence of popliteal reflux, thought to be a major contributor to the pathogenesis of chronic venous insufficiency, is associated with an increase in the rate of reflux as measured by VFI.

The measurements performed during tiptoe manoeuvres, however, did not contribute much to the assessment of these limbs. The ejection fraction has been claimed to measure the efficacy of the calf muscle pump. Christopoulos *et al.*[4] studied the ejection fraction in limbs with deep venous reflux and demonstrated that a good ejection fraction correlated with prevention of ulceration. The present study identified 30 limbs with popliteal reflux of which 15 had venous ulcers; the ejection fraction showed no significant difference between those with and without ulceration. The RVF, previously claimed to correlate well with the incidence of ulceration[4], showed substantial overlap of data between the clinical groups. This parameter has also been claimed to correlate with AVP[4], the accepted 'gold standard' measurement of venous insufficiency. No correlation was found between these two measurements in the present study ($r_S = 0{\cdot}04$).

Parameters that measure the rate of venous reflux (VFI, VFT_{90}) using air plethysmography may show useful trends in quantifying venous disease, but the relationship between volume measurements using air plethysmography and direct pressure measurements is less clear cut. Substantial overlap was found in the measurements of RVF between the groups of limbs examined and, in addition, the correlation between RVF and AVP was extremely poor.

The pressure–volume curve as a vein is distended is far from linear; initially the volume increases with minimal rise in pressure, then at higher pressures the volume increase is minimal for a large rise in pressure[5]. Limbs with less severe venous disease (i.e. low AVP) are examined at one place on the pressure–volume curve while those with more severe disease are examined at a point on the curve with a different gradient and thus a different pressure–volume relationship. This may be one reason why AVP and RVF do not correlate.

The RVF is not useful in assessing clinical severity of disease and this measurement does not correlate well with AVP, the accepted 'gold standard' of venous investigation. The rate of venous refilling is more quickly and simply measured using photoplethysmography[6]. It is concluded that air plethysmography does not fulfil some of the claims of previous reports. Assessment of RVF by air plethysmography did not correlate with AVP measurement and so should not be used as a substitute.

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Surgical workshop

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Aortic anastomosis made easier

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During repair of abdominal aortic aneurysm, the proximal graft–aortic anastomosis is usually created following the technique described by Creech[1] in 1966; the posterior wall of the aorta is not disturbed, thus providing a substantive bulk of tissue to which the graft can be sutured. Because of restricted access it is necessary to insert the needle into the posterior aortic wall and the graft separately before parachuting the latter into position. Moreover, when the posterior wall is smooth and flat, it is difficult to obtain adequate bites of tissue and to retrieve the needle easily.

The technique described in this paper was designed to allow simultaneous needle placement in the graft and aortic wall while maintaining the principles of the Creech method.

Surgical technique

The aneurysm sac is opened as in the standard method, transecting no more than two-thirds of the aneurysm neck and leaving the posterior aortic wall intact. The graft to be sutured to the proximal aorta is first reflected on itself 1·5 cm from its proximal end. A right-angled vascular clamp is placed half way along this folded section of the prosthesis to produce a 'heel' of graft below the clamp and an adequate lip above to 'take' sutures (*Figure 1*). The first assistant, standing on the patient's right, then places the clamp on the back wall of the aorta, pushing slightly cephalad so that the heel of the prosthesis creates a ridge of posterior aortic wall, which now lies adjacent to the end of the graft to be sutured. No extra access is required for this manoeuvre. Standing on the patient's left, the right-handed surgeon begins the anastomosis at the right side of the posterior aortic wall and sutures towards himself or herself, taking adequate bites of both posterior aortic wall and graft at the same time. The strength of the needle bites in the ridge of aorta is clearly visible both during the initial two or three passages of the needle, before the graft is firmly apposed to the vessel wall, and subsequently as the thread is held taut by the assistant 'following' the surgeon.

On completion of the posterior wall anastomosis, the right-angled clamp is removed and placed across the front of the graft, creating a space between the anterior graft wall and anterior aortic wall. The assistant surgeon, standing on the patient's right, now completes the anterior half of the anastomosis, suturing towards himself or herself from left to right (*Figure 1*).

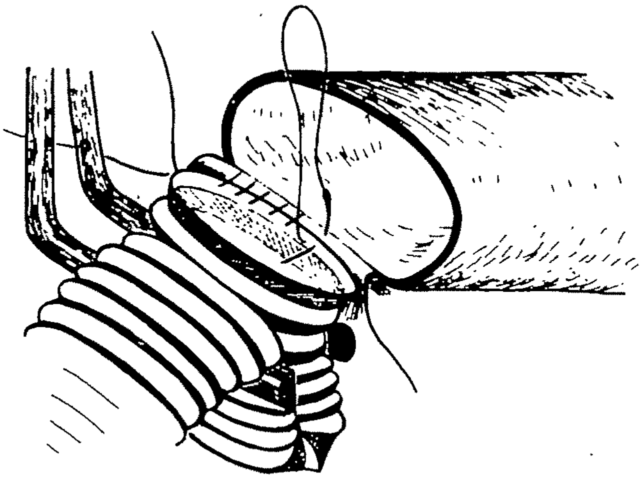

Figure 1 *The graft, reflected on itself and held by a right-angled vascular clamp, is pushed against the posterior aortic wall to create a ridge that facilitates suture placement*

Discussion

The method described of positioning the graft for the proximal anastomosis has been successful in over 50 transabdominal and retroperitoneal aortic aneurysm repairs in the past 2 years. When a ridge is created at the aneurysm neck the prosthesis can be placed against it, allowing simultaneous insertion of the needle through the aortic wall and graft. Deep bites can be taken in the aortic wall and the needle is easily retrieved, making the anastomosis easier to perform and more likely to be haemostatic and secure. Methods have been described for creating a ridge in a flat posterior wall, but these require mobilization of the posterior aortic wall with possible damage to the lumbar vessels[2]. In the present method, the principles of the Creech technique are adhered to, problems of access for needle insertion and retrieval are overcome and, by being able to insert deep accurately placed bites in the posterior aortic wall, we believe that the need to introduce further haemostatic sutures after completion of the anastomosis is reduced.

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Risberg retroperitoneal approach to the abdominal aorta

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In a study of the best approach to the infrarenal abdominal aorta, 47 patients were compared retrospectively: 15 underwent a standard transperitoneal incision, 15 a retroperitoneal left flank incision and 17 a new modified lateral pararectus incision, the Risberg approach. Operating time, length of postoperative intubation and hospital stay, mortality rate, morbidity rate and cost were assessed. There was a significant reduction ($P < 0.05$) *in mean(s.d.) operating time (141(21)* versus *198(41) min), intraoperative cross-clamping time (74(13)* versus *104(46) min) and postoperative intubation time (6·5(8·0)* versus *13·3(7·3) h) associated with the Risberg retroperitoneal incision compared with the left flank retroperitoneal route. There was also a significant decrease* ($P < 0.02$) *in mean(s.d.) postoperative intubation time (6·5(8·0)* versus *17·5(12·0) h), time after operation to discharge (11·0(2·4)* versus *17·3(7·6) days) and hospital cost (£4885(670)* versus *£7732(580)) associated with the Risberg incision compared with the transperitoneal approach. The Risberg incision gives better access to the infrarenal abdominal aorta while maintaining the advantages of other retroperitoneal approaches. This technique is recommended as the incision of choice for the retroperitoneal approach to the aorta.*

The transperitoneal approach with inlay graft replacement for abdominal aortic aneurysm (AAA) was described by Creech[1] in 1966 and is now the accepted and most widely applied surgical approach to the infrarenal aorta. However, over the past 30 years several surgeons have advocated the retroperitoneal approach for repair of AAA and aortoiliac occlusive disease, using a variety of incisions[2–5]. Several studies have shown the clinical superiority of the retroperitoneal over the transperitoneal route and recent evidence demonstrates reduced physiological disturbance with this technique. The retroperitoneal approach is associated with lower operative morbidity and mortality rates, fewer postoperative complications, and reduced hospital stay and cost[2,5–8]. However, debate continues as to the optimal retroperitoneal incision. The present retrospective study compared the standard transperitoneal route[1] with two retroperitoneal approaches: a left oblique flank incision[9] and a crescent-shaped left paramedian incision with an oblique extension on to the left chest wall, the Risberg incision[4].

Patients and methods

A total of 47 consecutive patients undergoing elective repair of infrarenal AAA were studied retrospectively. The patients were divided into three groups: 15 underwent aneurysm repair via a transperitoneal approach, in a further 15 repair was achieved using a left oblique flank incision and in 17 the Risberg incision was employed.

Assessment before operation

All patients underwent baseline laboratory investigations including full blood count, determination of levels of urea, creatinine and electrolytes, and coagulation screen. Chest radiography, electrocardiography, pulmonary function tests and radionuclide left ventricular ejection fraction estimation were used to assess coexistent cardiorespiratory disease. Ultrasonography and computed tomography were used to assess the size and extent of the AAA. All patients were comparable for age, sex, American Society of Anesthesiologists (ASA) grade, size of aneurysm and preoperative left ventricular ejection fraction (*Table 1*).

Surgical technique

All operations were performed by a vascular team led by two consultant surgeons. Invasive monitoring of pulse, blood pressure, central venous pressure, right atrial and ventricular pressure, and pulmonary wedge pressure was performed on all patients during surgery. The choice of incision was made by one of the two consultant surgeons, both of whom had extensive experience with transperitoneal and retroperitoneal approaches to the aorta. A Dacron tube graft (Unigraft, B. Braun, Melsungen, Germany) was used in all patients.

A standard transperitoneal approach was performed in 15 patients. After a midline incision extending from the xiphisternum to the pubic symphysis, a laparotomy was performed. The small bowel was displaced from the abdomen, exposing the aneurysm. After placement of vascular clamps on the infrarenal aorta just distal to the left renal vein and on the common iliac arteries, the aneurysm sac was incised and a Dacron tube graft inlaid into the sac using the Creech technique[1]. The native aneurysm sac was closed over the graft and the abdomen closed with a monofilament suture.

For the retroperitoneal left flank approach the patient was positioned in a semilateral position with the left side uppermost[5]. The incision extended from the lateral border of the rectus muscle anteriorly adjacent to the umbilicus to the 11th intercostal space posteriorly. The muscle layers were divided with cautery and the lumbar fascia incised posteriorly. The retroperitoneal space was developed and the left kidney

Table 1 *Details of 47 patients undergoing abdominal aortic aneurysm repair*

	Transperitoneal incision (*n* = 15)	Retroperitoneal incision	
		Left flank (*n* = 15)	Risberg (*n* = 17)
Sex ratio (M:F)	13:2	11:4	13:4
Age (years)*	66(7)	73(8)	71(8)
Anteroposterior aneurysm diameter (cm)*	4·7(1·0)	4·9(1·0)	4·7(1·0)
Left ventricular ejection fraction (%)*	53(8)	52(5)	49(12)
ASA grade II	10	11	10
Epidural anaesthesia	7	8	9

*Values are mean(s.d.). ASA, American Society of Anesthesiologists

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and ureter displaced anteriorly, exposing the aneurysm. Vascular clamps were placed and the AAA repaired using the Creech technique.

The Risberg incision[4] was first described in 1989. For this technique, the patient was placed in a semilateral position with the ipsilateral shoulder at approximately 60° to the horizontal. The skin was incised along the left linea semilunaris from just above the pubic symphysis to the left costal margin, where the incision was extended obliquely on to the left chest wall in the seventh intercostal space for approximately 8 cm (*Figure 1*). The fascia was incised down to the peritoneum along the length of the wound and, above the costal margin, the muscles were divided down to the ribs. Beginning distally the peritoneum was displaced medially, exposing the retroperitoneal space. The kidney and ureter were displaced medially to expose the aneurysm. The rest of the repair was performed using the standard Creech technique and the wound closed in layers using a monofilament suture.

After operation patients were transferred to the intensive care unit for ventilation, if required, and invasive monitoring. Perioperative epidural analgesia was administered in 17 patients. There was no difference in the epidural usage rate between the various groups (*Table 1*). The cost of hospitalization was estimated in the following manner. Each patient was in hospital for a mean of 3·5 days before surgery. After operation the patients were nursed initially in the intensive therapy unit followed by a recuperative period in a surgical ward. Costs were estimated at £250 per day for a surgical ward bed and £450 per day for an intensive therapy bed. Operating room costs were assumed to be similar for all three groups. Operating time, cross-clamping time, postoperative intubation time, number of days to discharge, mortality and morbidity rates, and cost were compared in the three groups of patients. Mean age, preoperative laboratory data and aneurysm size were compared using Student's *t* test. Fisher's exact test was used to compare the percentage of men, ASA grade, epidural usage rate and number of postoperative complications.

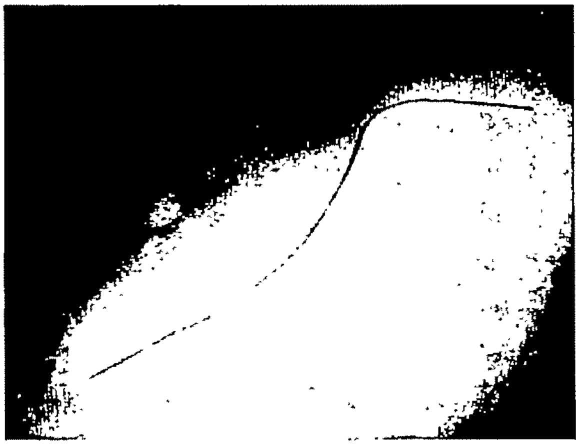

Figure 1 *The Risberg approach. The line of incision is lateral to the rectus abdominis muscle and extends obliquely on to the anterior chest wall*

Table 2 *Complications in 47 patients undergoing abdominal aortic aneurysm repair*

	Transperitoneal incision ($n = 15$)	Retroperitoneal incision: Left flank ($n = 15$)	Retroperitoneal incision: Risberg ($n = 17$)	Total ($n = 47$)
Mortality at 30 days	0	0	1*	1
Ileus	2	1	1	4
Atelectasis or chest infection	3	2	1	6
Wound infection	1	0	1	2
Cardiac arrhythmia	1	1	0	2
Peripheral embolus	1	2	0	3
Incisional hernia	0	0	1	1
No. of patients†	6	4	4	14

*Patient died from previously undiagnosed pancreatic carcinoma 25 days after operation. †Some patients had more than one complication

Results

There was one death, in the group undergoing the Risberg incision; the patient died 25 days after operation and at autopsy pancreatic carcinoma was found. The other complications encountered are summarized in *Table 2*. Fourteen of the 47 patients developed complications after AAA repair: six with the transperitoneal incision, four with the left flank approach and four with the Risberg incision. Eight complications (two major, six minor) occurred in six patients undergoing the transperitoneal incision; the two major complications were postoperative pneumonia and a peripheral embolus that required embolectomy. Six complications (one major, five minor) occurred in four patients in the group with a left flank incision; the major complication was a peripheral embolus that required embolectomy. One other patient in this group had evidence of peripheral microembolization but this did not require embolectomy. Of the five complications that developed in four patients after the Risberg incision, one was major and four minor. The major complication affected the patient described above who died. A further patient in this group developed an incisional hernia that did not require treatment.

Operating time was measured from skin incision to skin closure. The Risberg approach had a significantly ($P < 0\cdot02$) shorter operating time compared with the left flank incision (*Table 3*). The operating times for the transperitoneal and retroperitoneal approaches were not significantly different. The cross-clamping time was longest for the left flank incision. The Risberg and transperitoneal approaches had significantly ($P < 0\cdot05$) shorter cross-clamping times compared with the left flank incision but there was no significant difference in cross-clamping times between the Risberg and transperitoneal approaches (*Table 3*).

There was no significant difference in operative blood loss among the groups. All three groups had similar lengths of stay in the intensive care unit after operation (*Table 3*). The

Table 3 *Perioperative details, postoperative stay and hospital costs for 47 patients undergoing abdominal aortic aneurysm repair*

	Transperitoneal incision ($n = 15$)	Retroperitoneal incision: Left flank ($n = 15$)	Retroperitoneal incision: Risberg ($n = 17$)
Operating time (min)	164(43)	198(41)*	141(21)
Cross-clamping time (min)	72(18)	104(46)†	74(13)
Perioperative blood loss (ml)	1100(370)	1300(292)	933(586)
Postoperative endotracheal intubation (h)	17·5(12·0)*	13·3(7·3)*	6·5(8·0)
Intensive therapy unit stay (h)	71(31)	66(28)	67(27)
Postoperative hospital stay (days)	17·3(7·6)*	12·8(7·0)	11·0(2·4)
Hospital cost (£)	7732(580)*	5290(890)	4885(670)

Values are mean(s.d.). *$P < 0\cdot05$ *versus* Risberg incision; †$P < 0\cdot05$ *versus* Risberg and transperitoneal incisions (Student's *t* test) length of postoperative intubation was significantly ($P < 0\cdot02$) longer for the transperitoneal incision compared with the Risberg approach but not for the left flank incision. However, the duration of postoperative intubation was significantly ($P < 0\cdot05$) shorter in the Risberg approach compared with that of the left flank (*Table 3*).

The postoperative stay was significantly ($P < 0\cdot02$) shorter for patients undergoing the Risberg incision compared with those undergoing the transperitoneal incision. The Risberg approach also resulted in a slightly shorter postoperative stay than the left flank incision but this was not statistically significant. There was no significant difference in length of postoperative stay between patients undergoing left flank and transperitoneal incision. The cost of hospital stay was highest for the transperitoneal approach, with a significantly ($P < 0\cdot02$) lower cost for the Risberg incision (*Table 3*). A mean saving of £2800 per patient was made when the Risberg approach was used in preference to the transperitoneal route. There was little difference in the mean cost of the Risberg incision and that of the left flank approach.

Discussion

The first successful repair of an infrarenal AAA was reported by Dubois *et al.*[10] in 1952 using a thoracoabdominal incision with a retroperitoneal approach to the abdominal aorta. In 1963 Rob[2] reported a series of over 500 repairs of AAA using a retroperitoneal approach. Since then there have been several descriptions of the use of retroperitoneal approaches to the aorta for both elective and emergency aneurysm repair, but the technique has failed to gain wide acceptance in routine aortic revascularization[3,5,7,11,12]. The transperitoneal approach, described by Creech[1] in 1966, is currently the most widely applied surgical technique for repair of AAA. However, several authors have reported a reduced postoperative morbidity rate with retroperitoneal incision, specifically a decrease in the incidence of ileus with earlier return to oral feeding, fewer respiratory complications, reduced intubation time and decreased hospital stay and cost[2,5–7,11]. Sicard *et al.*[7] reported a saving of US$ 2587 per patient when using a left flank incision compared with a transperitoneal approach (mean(s.d.) US$ 12 549(778) *versus* US$ 15 136(905)).

A recent prospective randomized study comparing the transperitoneal and retroperitoneal routes showed no difference between the two[13]. The retroperitoneal approach used was a left flank incision as advocated by Sicard *et al.*[7] and Cambria and colleagues[13]. Although a multitude of retroperitoneal approaches has been described[2,4,9,14–16], to date no study has compared two different types of retroperitoneal approach. In the present study it was found that the Risberg incision, although slightly more extensive than the left flank approach, allowed easier access to the neck of the aneurysm and facilitated cross-clamping, which resulted in a shorter operating time. Both cross-clamping time and operating time were significantly shorter in patients undergoing the Risberg incision in comparison with those operated on by the left flank route. However, this better access and shorter cross-clamping time were associated with none of the disadvantages of the transperitoneal route and did not appear to reduce the physiological advantage obtained with other retroperitoneal approaches[8,17].

The complications seen when using the Risberg approach are noteworthy; the only death was in this group. The patient died from pancreatic carcinoma, which would probably have been detected had a transperitoneal route been adopted. Inability to perform a laparotomy is an inherent disadvantage of all retroperitoneal approaches. However, the incidence of serious pathology found coincidentally during AAA repair is small; the majority of reported patients with coexisting pathology have gallstones[18]. Another minor complication seen in patients undergoing the Risberg incision was an incisional hernia. Because of the nature of the incision the intercostal nerves supplying the rectus muscle must be cut and thus there is a risk of this complication. Attention to detail during wound closure may reduce this problem.

The present retrospective study has demonstrated the feasibility of performing a Risberg incision in most patients with AAA. It is believed that this route is superior to the left flank retroperitoneal approach; the Risberg incision should be considered in all high-risk patients undergoing aortic surgery. We agree completely with the view of Johnson and colleagues[19] that a retroperitoneal approach 'is not a difficult operation for the surgeon. It is without doubt a much easier operation for the patient'.

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Preoperative coagulopathy in ruptured abdominal aortic aneurysm predicts poor outcome

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In a prospective study of 50 consecutive patients undergoing operation for ruptured abdominal aortic aneurysm, a coagulation screen was performed on admission to hospital. Twenty patients with either a platelet count $<100 \times 10^9$/l or a prothrombin time $>1\cdot5$ times the control value had a mortality rate of 65 per cent (95 per cent confidence interval 45–85 per cent); a further 23 patients with normal screen results had a mortality rate of 9 per cent (95 per cent confidence interval 0–20 per cent) (P $<$ 0·001). *Seven patients, of whom three died, did not have an admission coagulation screen performed. Patient age in the study group did not have independent statistical predictive power. This study indicates that coagulopathy at the time of admission predicts poor outcome in patients with ruptured aortic aneurysm. Current management strategies are inadequate for the treatment of these patients, who can be rapidly identified on admission by means of platelet and prothrombin counts.*

Ruptured abdominal aortic aneurysm (AAA) continues to be associated with a high hospital mortality rate. The inpatient mortality rate[1–13] ranges from 21 to 70 (mean 49) per cent, despite the existence of specialized units employing rapid transport and resuscitation, and early surgical intervention by experienced personnel[5]. Current management of patients admitted to hospital with a diagnosis of ruptured AAA consists of rapid resuscitation to maintain systolic blood pressure above 80 mmHg, the use of pneumatic antishock garments and rapid transfer to the operating theatre. Although several previous studies have attempted to identify patients at high risk of poor outcome, no preoperative risk score has been shown to be generally effective or widely accepted[3,7,9–15]. Factors associated with increased mortality rate include advanced age[3,10,13], prolonged and profound hypotension[3,7,13,14], preoperative renal impairment[3,14], cardiac failure[10,11,14,15], chronic obstructive airway disease[7] and reduced level of consciousness[11].

Some studies have suggested that an association might exist between risk of death and pre-existing coagulopathy. Patients with evidence of disseminated intravascular coagulation (DIC) at presentation had mortality rates[16–18] of 11 of 15, eight of nine, and four of four. The present study was undertaken to find out whether a simple coagulation screen performed at admission could discriminate patients with a high risk of perioperative death from those with a low risk, in such a way as to provide a practical means for developing different management strategies for high-risk patients.

Patients and methods

A prospective study was carried out on 50 consecutive patients presenting to the accident and emergency department of a single hospital in whom a diagnosis of ruptured AAA had been made and who underwent operation. As soon as possible after admission, and before any blood or blood products had been transfused, blood samples were taken for a coagulation screen. This screen consisted of a platelet count and determination of the prothrombin time, activated partial thromboplastin time (APTT), thrombin time and plasma fibrinogen concentration.

The platelet count was measured by an automated analyser and checked manually to exclude platelet clumping. The prothrombin time was measured by standard methodology and expressed as the international normalized ratio (INR). A platelet factor III reagent (partial thromboplastin) plus particulate activator was used to determine the APTT (Automated APTT; Organon Teknika, Cambridge, UK)[19]. The thrombin time was measured using standard methodology that employs 3 units/ml calcium thrombin, adjusted to give clotting times of 9–11 s with normal plasma. The plasma fibrinogen concentration was measured using a modification of the Clauss technique[20].

Routine preoperative management consisted of establishing good venous access and, if the patient was hypotensive, infusion of crystalloids and colloids, and the application of a pneumatic antishock garment. When appropriate, patients were transfused with uncross-matched O-negative blood or cross-matched blood. Patients were transferred rapidly to the operating theatre. Transfusions of platelet concentrates and fresh frozen plasma were given during operation whenever a clinical diagnosis of established coagulopathy was made. All patients underwent emergency operation with aortic cross-clamping and insertion of a polytetrafluoroethylene vascular graft. Postoperative management was continued in the intensive care unit.

Patients were followed until death or discharge from hospital. A correlation was sought between the preoperative coagulation screen result and clinical outcome.

In the diagnosis of coagulation disorders, abnormal laboratory parameters can be demonstrated with simple tests such as platelet count, INR, APTT, thrombin time and fibrinogen level[21]. The main abnormalities are reflected by thrombocytopenia, prolonged prothrombin and thrombin times, and hypofibrinogenaemia[21]. A fibrinogen level below 1·0 g/l (normal range 1·5–4 g/l) and a platelet count $<100 \times 10^9$/l are regarded as virtually diagnostic, especially if associated with a generalized bleeding state[22]. For the purposes of the present study an abnormal coagulation screen was defined as a platelet count $<100 \times 10^9$/l, INR, APTT and thrombin time $>1\cdot5$ times the control values, and a plasma fibrinogen level $<1\cdot5$ g/l.

Statistical analysis was performed using separate Wilcoxon rank sum tests for analysis of age, hospital stay and individual components of the coagulation screen, comparing patients who died with those who survived. Multiple logistic regression analysis was used to test the combined effect of the different factors on mortality. Comparison of mortality rate and length of hospital stay in the two groups (presence or absence of coagulopathy) was by χ^2 analysis with Yates' correction.

Results

Fifty patients were entered into the study. As defined by the above criteria, 23 patients had normal and 20 abnormal admission coagulation screen results. Seven patients did not have a screen performed before blood transfusion was started or operation performed. It is felt that, in the clinical

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Table 1 *Immediate cause of death in the perioperative period*

Immediate cause of death	No. of patients	Time of death (days after operation)	Coagulation screen result		
			Normal	Abnormal	Not tested
Intraoperative haemorrhage	7	—	0	5	2
Myocardial infarction or cardiac arrest	3	0, 1, 9	0	2	1
Cardiac failure	4	1, 2, 4, 6	1	3	0
Multisystem organ failure	3	2, 6, 14	1	2	0
Cerebrovascular accident	1	14	0	1	0

Table 2 *Coagulation screen results in survivors and patients who died*

	Patient outcome		
	Survived ($n = 28$)	Died ($n = 15$)	P*
Platelet count ($\times 10^9$/l)	161 (61–290)	86 (35–146)	<0·001
International normalized ratio (patient:control)	1·5 (1·0–2·3)	2·3 (1·1–7·2)	<0·001
Fibrinogen level (g/l)	2·4 (0·5–6·8)	0·9 (0·1–2·6)	<0·001
Thrombin time ratio (patient:control)	1·2 (1·0–1·2)	1·3 (1·0–3·1)	n.s.
APTT ratio (patient:control)	1·3 (1·0–2·0)	3·5 (1·0–8·3)	<0·01
Age (years)	68 (55–81)	73 (58–80)	n.s.

Values are mean (range). APTT, activated partial thromboplastin time. *Wilcoxon rank sum test; n.s. not significant

Table 3 *Mortality rate in patients with differing patterns of coagulopathy*

Coagulation screen result	Mortality rate
Normal	2 of 23 (9)*
Abnormal	13 of 20 (65)†
INR >1·5 Platelet count >100 $\times 10^9$/l	0 of 4 (0)
INR <1·5 Platelet count <100 $\times 10^9$/l	1 of 4 (25)
INR >1·5 Platelet count <100 $\times 10^9$/l	12 of 12 (100)
Total	15 of 43 (35)

Values in parentheses are percentages. INR, international normalized ratio. *95 per cent confidence interval 0–20 per cent; †95 per cent confidence interval 45–85 per cent

circumstances surrounding admission of these critically ill patients, implementation of a research protocol in 86 per cent of cases is a reasonable achievement. Three of the seven patients who did not undergo screening died in the perioperative period, compared with 15 of 43 who did. There was no significant difference between these two groups, suggesting that patients in the unscreened group were not very different from those in the screened group. In addition, the unscreened group was further analysed by assuming a worst-case scenario in which all three patients who died would have had normal screen results had they been tested, and all four who survived would not (the probability of this scenario being true is about 0·007). In this case the mortality rate in the normal group would have been five of 26 (95 per cent confidence interval (c.i.) 7–39 per cent) compared with 13 of 24 in the abnormal group (95 per cent c.i. 33–74 per cent).

Overall, 18 patients died in the perioperative period; of these, 13 had an abnormal screen result, two a normal result and three no screen performed ($P < 0·001$ for the difference in mortality rate between patients with normal and abnormal screen results; 95 per cent c.i. of the difference between rates 32–80 per cent). The cause and time of death are shown in *Table 1*. As shown in *Table 2*, a low platelet count, raised INR and low plasma fibrinogen level were individually and collectively associated with a significantly increased risk of perioperative death. Thrombin time showed no significant difference between those who died and those who survived. A raised APTT lost its significant association with mortality rate when adjusted for platelet count or INR. Plasma fibrinogen level lost its significance when adjusted for platelet count. Patient age was not a significant independent variable.

There was a significant interaction ($P < 0·05$) in the logistic regression between platelet count and INR, suggesting that survival was significantly worse when both were abnormal than would be expected from the effects of each separately. This supposition was confirmed clinically with a 100 per cent mortality rate in patients with both a platelet count $< 100 \times 10^9$/l and a prothrombin time >1·5 times the control value (*Table 3*). Death was less likely when only one of these parameters was abnormal.

The length of hospital stay also showed a significant difference between the two groups. Patients with a normal preoperative coagulation screen result had a mean stay of 16 days, compared with 27 days for the seven with abnormal admission screen results who survived to leave hospital ($P < 0·001$).

Discussion

Ruptured AAA remains a major and increasing cause of death[23,24]. The present study was performed in an attempt to find a rapid method for early identification of patients with ruptured aortic aneurysm who have a high risk of death and for whom current management strategies are not sufficient. Admission coagulation screen results were analysed on the basis of earlier observations that, among patients with a high mortality rate, DIC is a frequent finding[16–18]. In addition, coagulation screens can be performed with relative ease and speed, and could be a practical method for the rapid identification of high-risk patients.

The results indicate that the presence of coagulopathy on admission to the accident and emergency department is a strong predictor for subsequent failure of standard management regimens: only two of 23 patients with normal screen results died compared with 13 of 20 with abnormal results. Although the numbers in this study are too small to be certain, it is interesting to see that abnormality in platelet count plus INR is associated with a very high mortality rate. In patients with only one abnormality, the prognosis was not so poor.

Previous studies have demonstrated an association between death from ruptured AAA and the presence of coagulopathy[16–18,25]. The present study, however, shows that it is possible to identify patients at high risk of death on admission to the accident and emergency department by determining the INR and platelet count.

Patient age did not show independent significance for mortality. However, this observation may have been influenced by undeterminable preadmission biases; for example, very elderly patients may not have been referred by primary care physicians or other hospitals.

None of the patients described had free intraperitoneal rupture of the AAA. Thus, the influence of established coagulopathy in this setting could not be evaluated. Prolonged preoperative hypotension may have contributed to the development of coagulopathy or to poor outcome. The time from rupture to arrival at the accident and emergency department could not be accurately determined. In all patients the time between arrival at hospital and entry to the operating theatre was less than 45 min, and for most it was less than 30 min.

The reason why coagulopathy predicts a poor outcome is not clear from the design or results of the present study. Although some of the deaths could clearly be linked to the presence of haemostatic failure, the link between the cerebrovascular accident 2 weeks after admission and coagulopathy on admission is obscure. The coagulopathy is possibly due to a consumptive disorder, reflecting the degree of tissue ischaemia before and during resuscitation, although this hypothesis will need to be proved in future studies. Some patients with asymptomatic AAA have low-grade DIC[16,26–28], and this may have contributed to the presence of coagulopathy. A simple dilutional coagulopathy arising during resuscitation before the blood sample was taken is improbable as no patient received more than 2 litres of colloid–crystalloid fluid intravenously before samples were taken. This volume is not associated with appreciable dilutional thrombocytopenia or hypofibrinogenaemia unless consumptive coagulopathy is also present[29]. None of the patients had a history of liver disease or was taking aspirin or anticoagulant medication before admission. Coagulopathy on admission may indicate a risk of excess bleeding at operation and can serve as a marker for ischaemic organ damage.

The present findings have important implications for the management of ruptured aortic aneurysm. Clearly, current management works well provided the patient is not in a high-risk group, but patients with pre-existing coagulopathy do badly, with an overall perioperative mortality rate of 65 per cent (95 per cent c.i. 45–85 per cent). This group can be identified rapidly on admission to hospital: it should be possible to perform a platelet count and INR within 30 min of arrival. On the basis of these observations, there is a need for prospective studies assessing the ability of therapeutic intervention to improve outcome in high-risk patients with ruptured AAA. Possible therapeutic interventions could include aggressive haemodynamic support, with provision of plasma and platelet transfusions to correct coagulopathies, and the administration of protease inhibitors which have proven benefits in bleeding disorders as shown in cardiac[30] and liver[31] transplant surgery. In addition, more extensive laboratory studies are required to analyse the mechanisms that contribute to the development and persistence of coagulopathy in these patients.

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Basic fibroblast growth factor accelerates wound healing in chronically ischaemic tissue

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The influence of subcutaneously injected recombinant human basic fibroblast growth factor (bFGF) on wound healing in normal ($n = 20$) *and ischaemic* ($n = 28$) *skin tissue was investigated. Standardized wounds (5 mm²) were created on the ears of hairless mice and treated for the first 3 days after wound creation with total doses of 720 ng* ($n = 24$) *and 4050 ng* ($n = 24$) *bFGF. The bFGF had no effect on wound healing in non-ischaemic tissue. In ischaemic skin, mean(s.d.) wound surface area after treatment with 720 ng bFGF was 1·6(0·9), 0·5(0·6) and 0·1(0·3) mm² compared with 2·8(1·0), 1·4(1·0) and 0·8(0·7) mm² for control wounds on days 7* ($P < 0.04$)*, 10* ($P < 0.03$) *and 13* ($P < 0.04$) *respectively. High-dose bFGF (4050 ng) reduced the mean(s.d.) wound surface area to 2·4(0·7) and 0·8(0·7) mm² compared with 3·9(0·6) and 2·1(0·8) mm² for control wounds on days 7* ($P < 0.006$) *and 10* ($P < 0.02$) *respectively. These results suggest that bFGF may be of use for the treatment of wounds in ischaemic tissue.*

The recent isolation of growth factors has provided new insights into embryogenesis and tumour growth. Such factors may also have a role in therapeutics by improving wound healing. Application of exogenous growth factors has been shown to influence positively wound healing in animal models and early clinical trials[1–6].

Basic fibroblast growth factor (bFGF), a potent mitogen for mesodermal- and neuroectodermal-derived cells[7], promotes the formation of granulation tissue when administered in subcutaneous sponges placed in rats[8,9]. This effect is thought to be caused by stimulation of angiogenesis[9–11], mitotic activity and recruitment of fibroblasts[9] resulting in higher levels of collagen deposition. It is known that bFGF affects collagenase secretion[12], thereby interfering with the process of remodelling in the late phase of wound repair, and induces regeneration of specialized tissues such as cartilage and bone[13,14].

This study was performed to quantify the effect of recombinant human bFGF on the healing of standardized wounds in normal and ischaemic skin tissue.

Materials and methods

Animal model

The ears of homozygous (*hr/hr*) hairless mice (8–12 weeks of age; 25–30 g) were used[15,16]. The mouse ear consists of two full-thickness layers of skin separated by a central layer of cartilage. Blood supply to the ear is provided by three vascular bundles entering the ear at its base.

For induction of ischaemia, wound creation, drug administration and measurements of wound surface area, the mice were immobilized in a plastic restrainer[15].

Induction of ischaemia

To render the ear ischaemic, two of the three principal neurovascular bundles (anterior and middle) were ligated 3 days before wounding using a 6/0 silk suture. A time lag of 3 days was chosen because pilot studies had shown that wound creation directly after ligation is followed by perforation of the ear in the wound area. Previous investigations[17] demonstrated that transcutaneous oxygen tension decreased from 24 to 6 mmHg after ligation and remained reduced throughout the follow-up period of 15 days. Wound closure in ischaemic tissue was significantly delayed for 3 days compared with wounds in normal ears[17,18].

Wound creation

Wounds were created as described by Bondàr *et al.*[18]. Under ether inhalation anaesthesia, the area selected for wounding on the dorsal side of the ear was marked with an O shaped ink stamp of diameter 2·5 mm. Using this mark a full-thickness dermal layer, down to but not including the cartilage, was excised with microscissors under an operating microscope (M 650; Wild Heerbrugg, Heerbrugg, Switzerland) to provide a standardized full-thickness wound of approximately 5 mm² in surface area. Wounds were created on both ears, one wound serving as a control.

Administration of growth factor

On 3 consecutive days, 80 or 450 ng recombinant bFGF (Progen, Heidelberg, Germany) dissolved in 1 µl phosphate-buffered saline (PBS) was injected subcutaneously into the wound edge using a hypodermic 32-G needle (no. 90032, outer diameter 0·23 mm; Hamilton, Bonaduz, Switzerland) and a microlitre syringe (no. 701 LTWG; Hamilton) at three preselected opposing sites (*Figure 1*). Total doses of 720 and 4050 ng bFGF were applied to wounds in normal and ischaemic tissue during the treatment. Identical volumes of PBS were administered to control wounds on the contralateral ear. Repeated

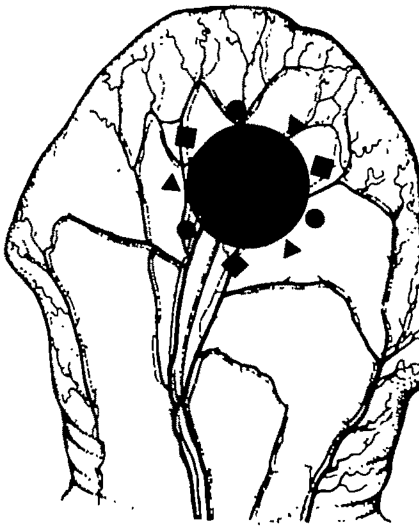

Figure 1 *Schematic diagram of mouse ear showing wound (large black circle) and sites of injection for days 1 (●), 2 (■) and 3 (▲)*

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injection was chosen as pilot studies had shown that single bFGF administration had no effect on wound healing in this model.

Measurement of wound surface area

While restrained in the observation platform, the mice were placed under an intravital microscope (Orthoplan; Leitz, Wetzlar, Germany). Using a videocamera (COHU 4410 SIT; COHU, San Diego, California, USA), the microscopic image of the ear (×57 magnification) was displayed on a monitor (CD 33; Barco Communications, Kortrijk, Belgium) connected to a digitizing board (Bit Pad One; Summagraphics, Munich, Germany). At this magnification, the wound occupied a single microscope field and could be seen in its entirety on the monitor. Observation of the microcirculation close to the wound edge was carried out at a magnification of ×560.

Scabs were removed before measurement of wound surface area. This method results in only a slight delay of re-epithelialization[19]. Wound edges were determined and traced. The area within the traced line (wound surface area) was calculated by a digital planimetric system integrated into the computer-assisted microcirculation analysis system[20].

Experimental design

In all, 48 animals were assigned to either the ischaemic ($n = 28$) or non-ischaemic ($n = 20$) group. Half of the animals in the ischaemic group received 720 ng bFGF and half 4050 ng. Of the non-ischaemic animals, ten received 720 ng and ten 4050 ng bFGF. In all animals the contralateral ear served as a control receiving identical volumes of PBS ($n = 48$).

Human bFGF or PBS was injected on days 1, 2 and 3 after wound creation; wound surface areas were measured immediately, on days 4, 7 and 10, and every third day thereafter until the wound had healed. A wound was considered to be healed when the tissue defect was completely re-epithelialized as determined by daily direct microscopic observation.

For morphological studies, animals were killed on days 7, 10 and 13. For sample preparation, a plastic catheter (outer diameter 0·61 mm; PP10, Portex, Hythe, UK) was inserted into the abdominal aorta. After incision of the inferior vena cava and administration of an initial 5-ml bolus of 2·5 per cent glutaraldehyde in 0·1 mol l^{-1} sodium cacodylate buffer (pH 7·4), the animals were continuously perfused for 20 min with an infusion pump (Perfusor V; B. Braun, Melsungen, Germany). The ears were harvested and specimens of the wound area prepared for histological and electron microscopic studies as described previously[15].

Statistical analysis

Statistical analysis was performed on a MicroVax III Computer using SAS Institute programs (SAS Institute, Cary, North Carolina, USA). For normally distributed results, values are given as mean(s.d.). Comparisons between treated and control groups were made using Student's t test for paired samples. Non-parametric values are given as median (interquartile range), using the Wilcoxon signed rank test for comparisons between groups. Both tests were accompanied by a Bonferroni–Holm correction for multiple test procedures. Statistical significance was accepted at $P < 0·05$.

Results

Macroscopic and microscopic observations

Macroscopic changes were observed as early as 2–3 days after the first injection of bFGF into the wound edge. The wound had a dark-red appearance suggestive of hyperaemia, which was most intense from day 7 to day 13 and thereafter decreasing. This response was limited to the area of injection. Tissue not adjacent to the injection site was unaffected. The ear increased in thickness at the injection site until the end of the period of observation.

Intravital microscopic observations at a magnification of ×560 revealed marked dilatation of venules and an increase in capillary diameter. Extravasated red blood cells were observed.

These changes were most pronounced in the group treated with the higher dose of bFGF (4050 ng) and were more distinct in ischaemic than non-ischaemic tissue. In animals without ischaemia, the lower dose of bFGF had little effect.

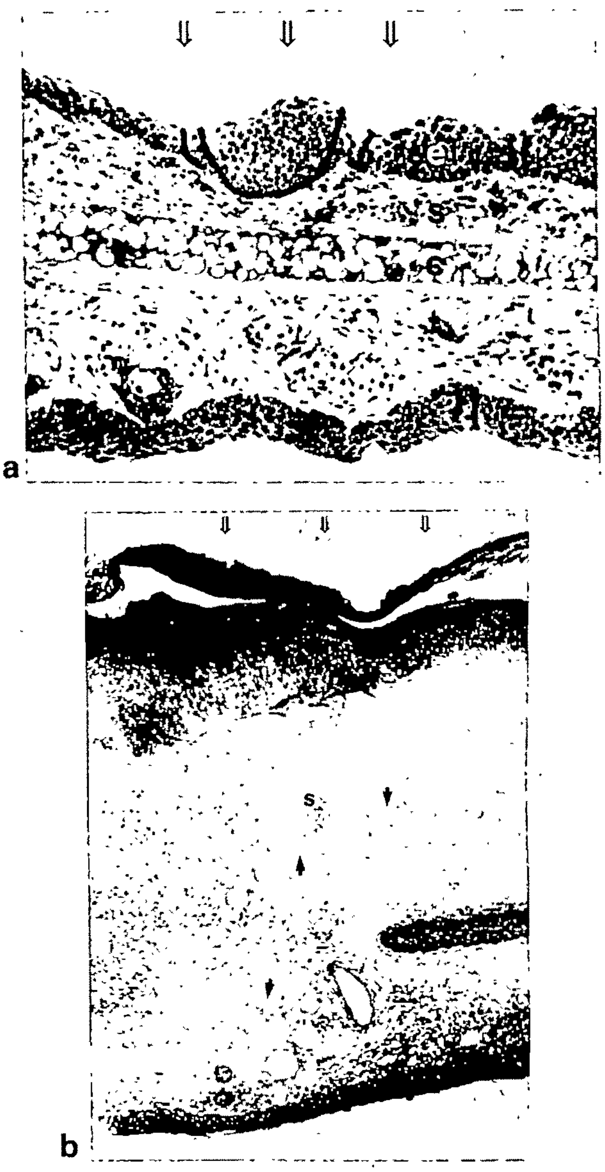

Figure 2 *Photomicrographs of wound specimens 13 days after wound creation on the dorsal part of the ear (open arrows). e, Epidermis; s, subepidermal layer; c, cartilage.* **a** *Normal wound after complete re-epithelialization. The cartilage layer is visible between the two skin layers. (Giemsa stain, original magnification ×100.)* **b** *Ischaemic wound treated with 4050 ng human basic fibroblast growth factor. The epidermal layer is enlarged by several cell layers and shows reactive acanthosis due to inflammatory reaction. The cartilage has grown on both sides by three cell layers. There is massive formation of granulation tissue with densely layered large fibroblasts. The vessels are dilated with irregularly formed, elongated and sinusoidal shapes (solid arrows). There are numerous new capillaries with thick endothelium and narrow lumina between bizarrely formed vessels. (Methylene azure II stain, original magnification ×100)*

Histology

Semithin 1-μm sections of specimens 7 days after wound creation and treatment with bFGF showed oedematous thickening of the epithelial layer as the result of an inflammatory reaction. In comparison with the untreated wounds (*Figure 2*), the subepidermal layer was characterized by a higher number of fibroblasts and mast cells, and polymorphonuclear leucocytes and erythrocytes in the extravascular space. The vessels adjacent to the wound and on the opposite, ventral side of the cartilage were dilated and swollen. Their number increased on both ventral and dorsal sides of the cartilage. By day 10 the subepidermal connective tissue was more thickened, and deposition of newly formed collagen fibres was detected on both sides of the cartilage layer. Fibroblasts increased in

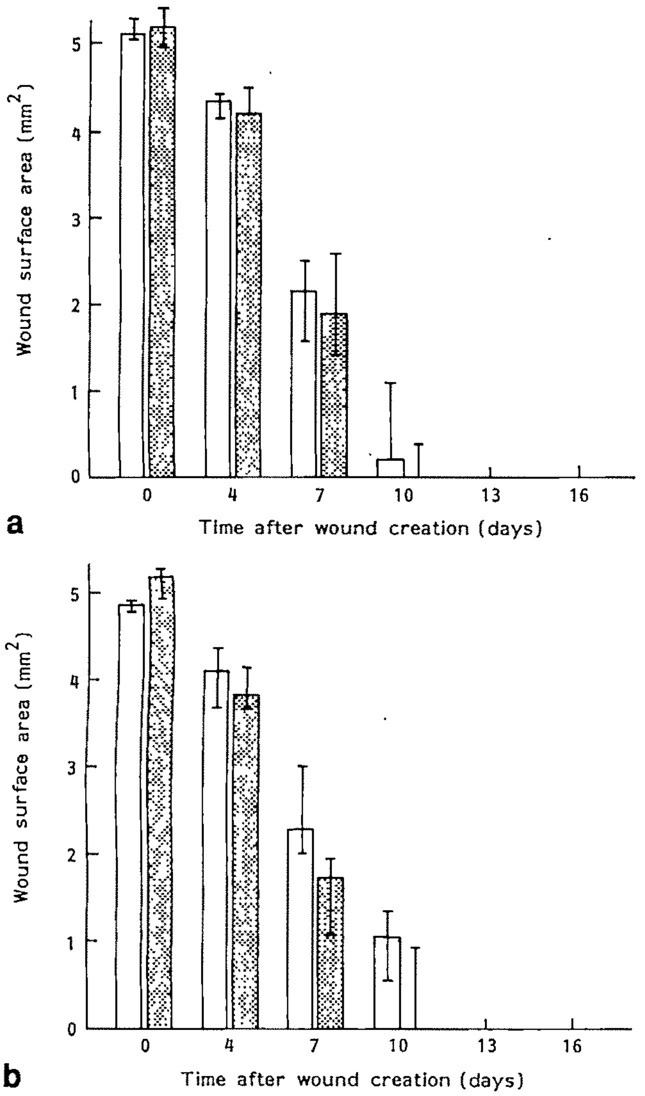

Figure 3 *Effect of* **a** *720 ng and* **b** *4050 ng human basic fibroblast growth factor (bFGF) on wound healing in normal tissue. Values are median (interquartile range).* □, *Control* (n = *10*); ▨, *bFGF* (n = *10*). P *not significant* (*Wilcoxon signed rank test with Bonferroni–Holm correction*)

Table 1 *Effect of human basic fibroblast growth factor on the duration of wound healing in normal and ischaemic skin tissue*

Tissue	No.	Total dose (ng)	Duration of wound healing (days)		P*
			bFGF	Control	
Normal	10	720	10·3(1·7)	11·3(1·6)	0·1
Normal	10	4050	10·7(1·4)	12·4(1·1)	0·02
Ischaemic	14	720	12·9(2·3)	14·9(2·7)	0·03
Ischaemic	14	4050	14·1(2·3)	15·9(2·1)	0·06

Values are mean(s.d.). bFGF, basic fibroblast growth factor. *Student's paired t test

number and size and some showed irregularly shaped nuclei. The cartilage had grown in thickness by two cell layers. By day 13 (*Figure 2*), these changes (except for the number of polymorphonuclear leucocytes) were more pronounced.

A large number of new vessels were detected by electron microscopy; these were characterized by a narrow lumen and thick endothelium with dense mitochondria and numerous free ribosomes, indicating synthesizing and proliferating activity. These vessels were surrounded by many fibroblasts that differentiated during angiogenesis into pericytes which embraced the new vessels. High vascular permeability during this process by extravasating erythrocytes and polymorphonuclear granulocytes was documented.

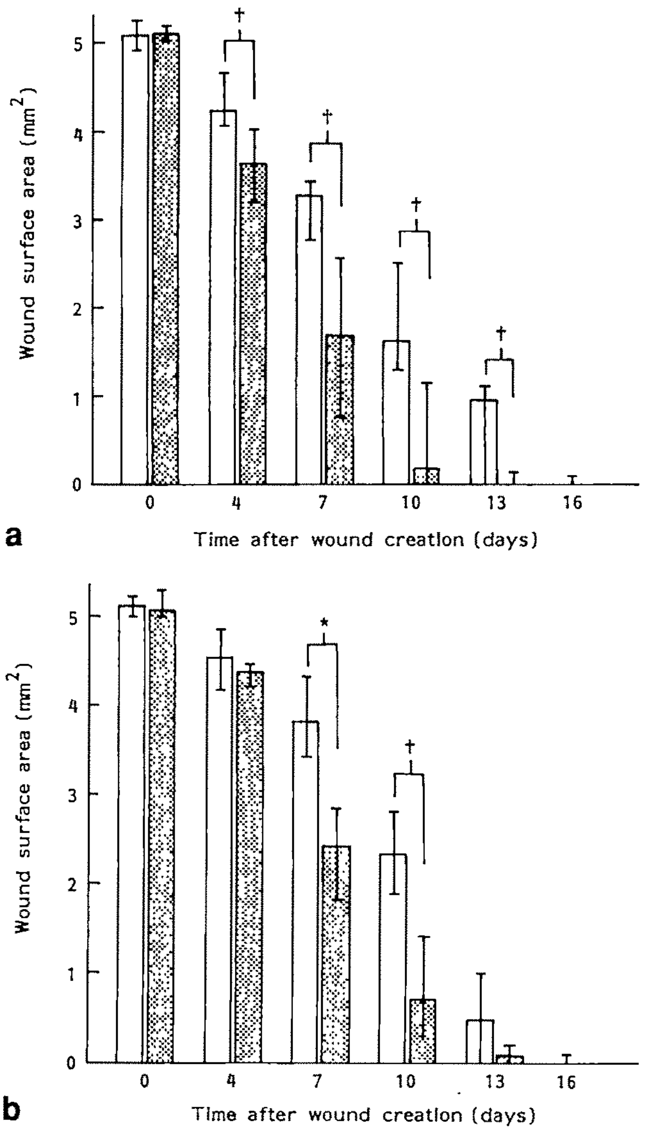

Figure 4 *Effect of* **a** *720 ng and* **b** *4050 ng human basic fibroblast growth factor (bFGF) on wound healing in ischaemic tissue. Values are median (interquartile range).* □, *Control* (n = *14*); ▨, *bFGF* (n = *14*). $^*P < 0.01$; $^\dagger P < 0.05$ (*Wilcoxon signed rank test with Bonferroni–Holm correction*)

Wound surface area

In non-ischaemic ear tissue, neither dose of bFGF reduced wound surface area at any time (*Figure 3*). Wounds treated with the high dose, however, were re-epithelialized 1·7 days earlier than were control wounds (*Table 1*).

In ischaemic tissue, the low dose of bFGF (720 ng) resulted in a significant reduction in wound surface area (*Figure 4*) on days 4, 7, 10 and 13 compared with control wounds. Wound closure was accelerated by 2·0 days in this group (*Table 1*). The high dose (4050 ng) caused a significant reduction in wound surface area (*Figure 4*) at days 7 and 10 compared with controls. Overall healing time was shortened from 15·9 to 14·1 days (*Table 1*).

Discussion

This study was undertaken to investigate the influence of bFGF on the healing of standardized wounds in normal and ischaemic skin. The results demonstrate that local application of bFGF has no influence on wound healing in normal tissue, but improves healing under conditions of ischaemia. This effect was due to marked stimulation of angiogenesis and increased formation of granulation tissue including growth of the epidermal, subepidermal and cartilage layers. Stimulation of endothelial cells, keratinocytes, fibroblasts and chondrocytes by bFGF has been shown by others in *in vitro* and *in vivo* experiments[7,10,11,14,21–24]. Furthermore, bFGF has stimulatory effects on the secretion of collagenase[10,12,25] and plasminogen activator[10,25,26] by competent cells, both of which are important for the migration of endothelial cells or fibroblasts through tissue barriers such as basal membranes and the extracellular matrix[27].

The present positive effect of human bFGF on wound healing in ischaemic tissue only is an interesting finding. In the experiments of Tsuboi and Rifkin[28], bFGF had no effect on wound healing in normal mice, whereas treatment of wounds in diabetic animals resulted in a significant response of all observed dermal parameters. These authors speculated that in normal mice the amount of endogenous growth factor was sufficient to achieve optimal wound healing, thereby limiting the efficacy of exogenous bFGF.

It may be that, under ischaemic conditions, the reduced washout of bFGF from the site of injection secondary to impaired microvascular perfusion produces higher effective concentrations of the growth factor for an extended period of time. In normal wounds bFGF disappears rapidly, with only 10 per cent of the initial dose remaining 4 h after application[9].

Differences in the extracellular milieu could also lead to variation in the expression of FGF receptors or their affinity to bind bFGF. It has been demonstrated *in vitro* that the release of bFGF and the number of bFGF receptor molecules on the cell surface is dependent on cell density in the culture[29,30]. Embryological studies have revealed that the levels of bFGF receptor expression vary during the differentiation process, suggesting that the variation plays an important role in the response of cells to the polypeptide[31]. Compared with normal tissue, higher levels of lactate, a low pH and reduced transcutaneous oxygen tension are found in ischaemic tissue. Although the influence of these parameters on the stimulatory activity of bFGF has not been determined, they may influence the interaction between bFGF and its receptor.

In summary, the present data indicate that bFGF has the ability to interact with different steps of the wound healing process and thus may be of value in the treatment of patients with impaired wound healing such as that secondary to ischaemic disease.

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Case report

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Survival after retroperitoneal necrotizing fasciitis

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Necrotizing fasciitis remains an uncommon cause of severe morbidity and high mortality in surgical wards. When it involves retroperitoneal tissues, the course is almost invariably fatal[1].

A patient is reported with retroperitoneal necrotizing fasciitis who presented with an acute abdomen and survived following early but limited operation and aggressive antibiotic manipulation. Success can be attributed to early diagnosis and rapid intervention.

Case report

A 74-year-old diabetic woman was admitted with a 12-h history of severe central abdominal pain and persistent bilious vomiting. Her complicated medical history included central retinal vein thrombosis, an operation for pituitary tumour (following which she had right hemiparesis and epilepsy), atrial fibrillation and hypercholesterolaemia. Medications included thyroxine 50 mg daily, hydrocortisone 20 mg twice a day, gliclazide 80 mg twice a day, phenytoin 300 mg at night, Burinex K (Leo Laboratories, Princes Risborough, UK) one tablet daily and digoxin 125 μg daily. On examination the woman had toxaemia and was pyrexial (38·5°C), with a regular but rapid pulse (120 beats min^{-1}) and a blood pressure of 105/50 mmHg. Abdominal palpation revealed generalized tenderness and guarding, and bowel sounds were present. She had a leucocytosis of 18·5 × 10^9 l^{-1}, blood urea level of 10·3 mmol l^{-1} and serum potassium concentration of 5·5 mmol l^{-1}. The blood glucose level was 8·9 mmol l^{-1} and that of serum amylase was normal. Abdominal radiography revealed a centrally placed dilated segment of bowel and there was no evidence of free intraperitoneal air. A diagnosis of peritonitis was made, and emergency laparotomy was undertaken within 2 h of admission.

At laparotomy there was neither visceral perforation nor generalized peritonitis. The only abnormality was in the pelvis, where induration and blackish discoloration of retroperitoneal tissues was seen. Opening the pelvic peritoneum produced the characteristic pungent odour of putrefaction. Pelvic retroperitoneal tissues were oedematous and necrotic. A careful search of the rectosigmoid colon, pelvic organs and bladder did not reveal a perforation or focus of sepsis. There were no colonic diverticula. An extensive surgical debridement would have required pelvic exenteration and abdominoperineal resection. This procedure was considered inappropriate, so faecal diversion was undertaken by means of sigmoid loop colostomy followed by pelvic peritoneal lavage and drainage of the pararectal space.

The patient was started on cefotaxime, metronidazole and flucloxacillin before operation together with intravenous hydrocortisone, and these drugs were continued in the intensive care unit. She had a stormy postoperative course at first with supraventricular tachycardia and high pyrexia. After 24 h there was redness and induration spreading up both flanks and foul-smelling discharge from the drain. Prognosis at this stage seemed dismal. The bacteria isolated from the retroperitoneal tissues and the drainage fluid were *Escherichia coli* and *Streptococcus faecalis*, so the antibiotics were changed to vancomycin and ceftazidime. Contrary to expectation, the patient's condition improved rapidly over the next 24 h and she was returned to the ward. The woman continued to improve, was discharged after 2 weeks back to her nursing home and remains well 6 months later. Full investigation of the pelvic organs had revealed no cause for the massive pelvic sepsis amounting to soft tissue necrosis. There had been no vaginal douches or enemas in the period leading up to the illness.

Discussion

The main factors responsible for improved survival rates in necrotizing fasciitis are early diagnosis, rapid and aggressive debridement, broad-spectrum antibiotic cover, and nutritional and systemic supportive measures[2–6]. The patient discussed presented early with signs suggestive of peritonitis, and the diagnosis of retroperitoneal necrosis came to light at an emergency laparotomy. Adverse factors including advanced age, pituitary insufficiency, diabetes mellitus and the retroperitoneal site of sepsis indicated a poor prognosis. It seemed unlikely that the patient would survive pelvic exenteration, and thus faecal diversion, pelvic lavage and drainage was undertaken as a compromise. Broad-spectrum antibiotic cover and steroid replacement was instituted promptly. In the absence of a clinical response, the antibiotics were changed the next morning. The availability of bacterial isolates allowed the use of specific cover. The combination of early intervention and appropriate antibiotic therapy contributed to the successful outcome.

Woodburn and colleagues[1] recently reported a series of five patients with cutaneous manifestations of extensive retroperitoneal fasciitis. Late presentation or delayed diagnosis are responsible for the adverse outcome. As in other anatomical sites affected by necrotizing fasciitis, retroperitoneal infection may not always lead to a fatal outcome if early diagnosis is made. Appropriate intervention, both surgical and bacteriological, may even allow a lesser surgical procedure to be adopted.

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Computed tomography in the management of blunt abdominal trauma in children

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Sixteen children with suspected abdominal injury were reviewed. All underwent plain abdominal radiography and computed tomography (CT). Fifteen CT scans showed an abnormality, and the abdominal radiograph was abnormal in seven cases. Eight patients also underwent abdominal ultrasonography, and six scans failed to demonstrate an abnormality. Only two patients required laparotomy, one for a ruptured left diaphragm and one for a major renal injury. These results support the use of CT as the optimal method for assessing the stable child following blunt abdominal trauma.

Immediate laparotomy is required for children with abdominal injury who remain unstable in spite of efforts to correct hypovolaemia[1]. However, current paediatric surgical practice is to avoid laparotomy in patients who are stable unless there are specific indications for operation. It is important, therefore, to establish the presence and nature of any intra-abdominal injury accurately and rapidly by non-surgical means.

Children with abdominal trauma present in one of three broad categories: those with clinical evidence of an abdominal injury; those who are unconscious and have a high risk of abdominal trauma; and those who are shocked on presentation with no obvious cause for the shock[2,3]. The key to recognizing abdominal trauma is repeated clinical assessment, but this will not identify the nature of the injury. The Advanced Trauma Life Support (ATLS) system advocates diagnostic peritoneal lavage[1], but this has significant drawbacks, especially in children[4–6]. Abdominal ultrasonography has a high false-negative rate in blunt abdominal trauma[7].

An extensive review from the Children's National Medical Center, Washington, DC, has confirmed the efficacy of computed tomography (CT) for assessing the abdomen in the multiply injured child[8]. Because no such data have been published from a major paediatric surgical centre in the UK, the present study was undertaken to review experience with CT in the management of blunt paediatric trauma.

Patients and methods

Sixteen children who presented to the Accident and Emergency Department of the Royal Liverpool Children's Hospital Alder Hey between January 1989 and May 1992 with suspected blunt abdominal injury were reviewed. All were haemodynamically stable or in hypovolaemic shock that was easily corrected, and remained stable thereafter. Patients had a history or signs of abdominal injury, or were unconscious with a high risk of abdominal trauma or were initially shocked without an obvious cause for the shock. Severely injured children with persistent shock who required immediate laparotomy and/or thoracotomy were excluded, as were those with isolated head injury who were conscious, haemodynamically stable and had no clinical evidence of abdominal injury. Initial management followed ATLS guidelines. All patients underwent plain radiography of the lateral cervical spine, chest, abdomen and pelvis, followed, after stabilization, by abdominal CT. Findings were reviewed and correlated with the subsequent management and outcome.

CT was performed using a double-contrast technique. After emptying of the stomach, a solution of 2 per cent water-soluble contrast (iopamidol 300) was given via a nasogastric tube in an age-related dose (infants, 50–100 ml; children, 250–500 ml; adolescents, 500–1000 ml) 20–30 min before scanning to allow time for the contrast to enter the proximal small bowel. At the start of the abdominal scan (following CT of the head, if performed) a 2 ml/kg bolus of prewarmed intravenous contrast (iopamidol 300) was injected. Scanning was performed with contiguous cuts through the liver and kidneys (8-mm sections), then alternate sections down to the pubic symphysis. All scans were supervised and interpreted by a consultant paediatric radiologist. Eight patients underwent abdominal ultrasonography, performed before CT. Other investigations were performed as dictated by the clinical circumstances, for example chest or cranial CT.

The progress of each patient was reviewed, including haemodynamic stability immediately before and after scanning, and any subsequent operation performed.

Results

There were 13 boys and three girls, aged from 4 months to 15 years (mean 7 years 9 months). The injuries resulted from a road traffic accident in ten children and a fall from a height in six.

Eleven children had an isolated abdominal, pelvic or lower thoracic injury; all of these had clinical symptoms or signs relevant to the injury and underwent abdominal CT. None of this group was unconscious, shocked or required ventilation. Five children had multiple injuries; of these, all had a severe head injury (Glasgow Coma Score < 10), four a thoracic injury and two a high cervical fracture. Four patients required ventilation. Three of these five children were shocked at initial presentation but remained stable after appropriate colloid and blood transfusion; none of these three had specific clinical evidence of abdominal trauma but two had an injury demonstrated by CT. The other two children in this group were not shocked but had a history or signs suggestive of abdominal injury, which was confirmed by CT.

The plain abdominal radiograph was normal in nine of the 16 patients; only one of these had a normal CT scan (*Table 1*). Of the seven abdominal radiographs that were abnormal, three demonstrated a pelvic fracture and no further information was provided by CT. Of the remaining four abdominal radiographs, two showed loss of the psoas shadow (one of which was associated with a fracture of the transverse process of L4), one showed a soft tissue mass in the left flank, and one revealed a fracture of the left ninth rib. These four patients had a splenic fracture detected by CT.

Abdominal ultrasonography was performed in eight patients (*Table 1*). The ultrasonography and CT findings concorded in two patients, while in the other six ultrasonography failed to detect a significant injury of the liver (one patient), spleen (three), kidney (one), and both spleen and kidney (one).

Of the 16 abdominal CT scans, only one was normal. Thi was in an unconscious shocked patient who had no abnorma abdominal signs; chest CT revealed a haemothorax as the caus of hypovolaemia. Three CT scans showed an isolate retroperitoneal or pelvic haematoma, each of which wa secondary to a pelvic fracture and might have been predicte

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Table 1 *Diagnosis on imaging studies for abdominal trauma in 16 patients*

	No. of patients studied	Normal	Intraperitoneal fluid	Retroperitoneal haematoma	Organ injury
Plain abdominal radiography	16	9	0	1	0*
Ultrasonography	8	1†	4	0	3‡
Computed tomography	16	1§	2	3	10

*Four radiographs demonstrated rib, pelvic or transverse process fractures; †missed splenic fracture; ‡renal injury in one patient was identified but not a coexisting splenic injury; §confirmed by the clinical course

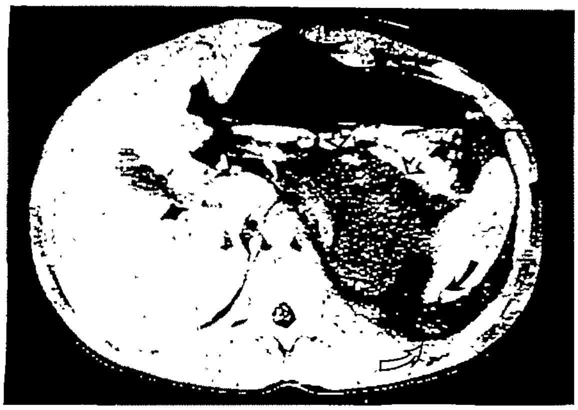

Figure 1 *Abdominal computed tomography with oral and intravenous contrast agents showing a non-functioning left kidney with a retroperitoneal haematoma (⇨) indicating a major renal hilar injury. A laceration of the lower pole of the spleen (➔) with surrounding haemoperitoneum (⇨) is seen*

from the initial plain radiograph. Five CT scans showed a single abnormality, namely four fractured spleens and one posterior liver contusion. The seven remaining scans showed injuries to both the spleen and left kidney in four patients, a traumatic rupture of the left hemidiaphragm with cephalad displacement of the left kidney in one, and haemoperitoneum without an obvious cause in two. In all, nine CT scans showed haemoperitoneum, seven of which were associated with an identifiable intra-abdominal injury. In two of the eight patients with a splenic laceration, no haemoperitoneum was seen on CT.

One of the nine patients with a haemoperitoneum underwent laparotomy. This was performed primarily for a fractured non-functioning left kidney which was removed because continuing haemorrhage led to a rapidly expanding haematoma (*Figure 1*). The haemoperitoneum arose from an associated splenic laceration that in itself did not require intervention. One other patient underwent laparotomy, to repair a tear of the left hemidiaphragm.

Fourteen of the 16 children did not undergo operation. Twelve made a full recovery (including the patient with a normal abdominal CT scan), one died from severe head trauma and one was quadriplegic after a high cervical fracture–dislocation.

Discussion

There are three criteria for abdominal CT in the injured child: (1) when abdominal injury is suspected clinically and the patient is either haemodynamically stable or hypotensive on admission and remains stable after resuscitation; (2) when there is a risk of abdominal injury but the patient is unconscious and cannot be assessed clinically; and (3) when the patient is initially shocked and, although subsequently stabilized, has no obvious extra-abdominal cause for the initial hypovolaemia[8]. CT is not indicated for the child who remains haemodynamically unstable despite intensive resuscitation, or who has an extra-abdominal life-threatening injury such as intracranial haematoma; these patients require immediate operation[1].

This review of experience with CT based on the above criteria illustrates the invaluable contribution of the method to the management of injured children. It should be noted that, by utilizing the information gained from such scans, no unnecessary laparotomy was performed. There was no morbidity or mortality attributable to the time spent stabilizing the patient and performing CT.

To aid assessment of the abdomen, all severely injured patients should initially undergo supine plain radiography of the chest, abdomen and pelvis to look for bony injury, pneumoperitoneum, excess intraperitoneal fluid and other pointers to intra-abdominal injury. In the authors' experience there is a high proportion of false-negative radiographs but if an abnormality is detected, particularly loss of the psoas shadow or an injury to the lower ribs or transverse process of a lumbar vertebra, there is a high likelihood of associated injury to the spleen or kidney.

Abdominal ultrasonography is often employed in the assessment of injured children. The advantages of ultrasonography are that there is no exposure to radiation and that it may be performed in the emergency room with ease and speed. Disadvantages in the traumatized patient are that access to the abdomen may be hampered by dressings, and scanning may be obscured by intestinal gas, especially in the presence of ileus. The retroperitoneum is not well visualized by ultrasonography, with the exception of the kidneys. Furthermore, the procedure is operator dependent and, in the authors' experience, inferior to CT in specificity and sensitivity. Ultrasonography was performed before CT in eight of the present patients but concurred with CT results in only two. In the remaining six children, ultrasonography failed to detect significant injuries to the liver, spleen and kidney. No injury demonstrated by ultrasonography was not apparent on CT.

Diagnostic peritoneal lavage is advocated by the ATLS system for assessing the abdomen in adults who fulfil the above criteria for CT. In our view, lavage is contraindicated in children for the following reasons. First, while lavage can reliably detect haemoperitoneum, that in itself is not an indication for laparotomy in children[6]. Furthermore, estimation of blood content in the aspirate is subject to wide variation, especially by less experienced surgeons who are more likely to advocate an aggressive surgical approach[6]. Second, lavage is traumatic and in an apprehensive injured child renders subsequent clinical evaluation of the abdomen difficult. Third, on CT, intraperitoneal fluid from the diagnostic lavage is indistinguishable from blood; this substantially reduces the value of subsequent CT. Fourth, lavage should be performed only by the surgeon who will undertake the laparotomy, should this be indicated[1], and should not be carried out unless positive findings will lead to laparotomy. Therefore, diagnostic lavage should not be performed at a district hospital if the patient is likely to be transferred to a paediatric centre for surgical management or intensive care. The use of lavage is likely to lead to an increased rate of emergency laparotomy[6,9], which is contrary to the current trend towards non-operative management of most intra-abdominal injuries in children. The only situation in which diagnostic peritoneal lavage may be justified is when the child may have an abdominal injury but requires immediate operation for extra-abdominal trauma (usually to the head) and in whom clinical and CT assessment of the abdomen is not possible.

Previous studies support the findings of this review; the sensitivity and specificity of CT approach 100 per cent for injuries of the liver, spleen and kidneys, when correctly carried out and interpreted by experienced personnel[2,3,10,11]. CT is less accurate for early identification of injuries to the pancreas; increasing serum amylase and lipase levels should raise suspicion of a pancreatic injury, particularly if the mechanism of injury is appropriate, and in this situation ultrasonography may be helpful. Repeat CT after 24 h is likely to demonstrate the pancreatic injury[12]. There is no reliable imaging technique for demonstrating injury to the intestine or mesentery except when pneumoperitoneum is seen on abdominal radiography. By using CT, with enteral contrast to opacify the gut, the likelihood of identifying a perforation of the stomach, duodenum or proximal jejunum is increased. Nevertheless, there is no substitute for repeated clinical examination to detect these injuries[4,8].

CT of the abdomen is useful in the patient who has a head injury and requires ventilation. Provided the patient is haemodynamically stable, it is more efficient and reliable to perform abdominal CT immediately after CT of the head, rather than waste time with abdominal ultrasonography in the accident and emergency department. Two points regarding emergency abdominal CT must be emphasized: the intravenous contrast agent must not be given until CT of the head has been completed, and injured patients undergoing CT must be closely monitored, with anaesthetic, surgical and nursing staff in attendance and full resuscitation equipment available in the radiology department.

The move towards a non-operative approach for paediatric intra-abdominal injury was prompted by recognition of overwhelming postsplenectomy sepsis[13,14] and the clinical experience that 90 per cent of injured spleens will stop bleeding spontaneously[15]. Similarly, 90 per cent of children with hepatic injuries do not require operation, although 10 per cent will develop a significant complication such as a biliary leak or haemobilia[16,17]. Exploration of an injured kidney is mandatory only when there is uncontrolled bleeding; nephrectomy is the usual outcome[18]. Renal artery occlusion is a relative indication for emergency operation since the renal salvage rate is extremely low[19]. For a major parenchymal tear involving the collecting system, the authors prefer delayed exploration when the risk of bleeding is low and demarcation of devitalized tissue is clearer. In all patients the possibility of multiple organ injury must be borne in mind.

In conclusion, diagnostic peritoneal lavage is rarely indicated in paediatric blunt trauma, ultrasonography is unreliable and CT is the imaging method of choice. Apart from shocked patients who require immediate operation, all others should undergo CT with intravenous and intragastric contrast agents when they are stable. If CT is not available, the child should be transferred to a paediatric surgical centre after stabilization. No investigation is a substitute for repeate careful clinical evaluation.

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Transatlantic perspectives of trauma systems

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The need for centralized management of acute trauma was evaluated in a 1-year prospective study in Northern Ireland. All patients with an Injury Severity Score >15 who reached hospital alive were included. The sample population was approximately 1 million people. A total of 239 patients entered the study, of whom 74 died. An audit panel considered that 3–15 per cent of deaths were preventable. There was no significant difference in the preventable mortality rate between any hospital or groups of hospitals. There was a high level of consultant involvement, especially in small hospitals. A system in which patients with acute trauma bypass the nearest hospital to reach a trauma centre may be neither beneficial nor cost-effective in Northern Ireland. Upgrading of the present system with stabilization of the patient and emergency surgery at the nearest hospital before transfer is recommended.

Recent research in the UK has shown that trauma care is in need of improvement[1]. In the USA, small hospitals dealing with low numbers of seriously injured patients have relatively more preventable deaths than large hospitals handling more patients with trauma[2,3]. All victims of trauma with potentially serious injuries were recommended to bypass small hospitals to reach a trauma centre where they would receive optimal resuscitation and emergency surgery. It has been proposed that the UK should adopt the American model but measures taken to improve trauma care must reflect differences in population, the amount of trauma and standards of care, as well as cost-effectiveness. A prospective review of major trauma was therefore undertaken to examine this issue.

Northern Ireland is a health region in the UK with a population of 1·5 million served by 19 acute hospitals. Apart from a small number of terrorist incidents the spectrum of trauma, patient demographics and variety of hospitals is similar to those of the other health regions in the UK. It has the advantage that patients can easily be followed as they are not transferred to hospitals outside the region.

Patients and methods

Twelve of the 19 hospitals were chosen on a stratified random basis to include small (<20000 new patients per annum attending the accident and emergency department) and large, rural and urban hospitals from a catchment population of approximately 1 million people. From 1 August 1990 data were collected prospectively for 1 year on all injured patients with an Injury Severity Score (ISS) >15 who reached the chosen hospital alive.

Recorded details included mechanism of injury, prehospital care and times, patient details, Revised Trauma Score (RTS) on arrival, ISS, personnel in the accident and emergency department, time of arrival, time to operating theatre, resuscitative and operative management, and follow-up. TRISS (Trauma and Injury Severity Score, age combination index) and ASCOT (A Severity Characterization of Trauma)[4] probabilities of survival, calculated from the RTS and ISS combined, were determined.

Patients who died with a prior probability of survival ⩾25 per cent were reviewed by a panel consisting of one specialist each from general surgery, accident and emergency, anaesthetics, neurosurgery and intensive care. The five assessors were blinded to patient, doctor and hospital identity, and made independent judgements in each case. They were asked to score the deaths as preventable or not (probability of survival >50 per cent or ⩽50 per cent respectively). The assessors were also asked to predict the degree of mental and physical disability they would expect the patients with preventable death to have had 2 years after the accident, had they survived. A scale of 0–10 was used, 0 representing persistent vegetative state and 10 previous level of function. The panel members were asked to note in each case which of the following changes would help to prevent similar deaths in the future: (1) Advanced Trauma Life Support training; (2) consultation with senior personnel; (3) shorter time to surgery; (4) specialist at hand; and (5) other.

χ^2 analysis with Yates' correction and Student's *t* test were used for statistical purposes.

Results

A total of 239 patients with an ISS >15 were included; 74 subsequently died in hospital. Patient demographics, mechanism of injury and mortality figures are shown in *Tables 1* and *2*. Fifty-four deaths were assessed; autopsies were obtained for 52. The conclusions of the audit panel are shown in *Tables 3* and *4*. Depending on the level of observer agreement the preventable mortality rate ranged from 3 to 15 per cent, or from 3 to 16 per cent when terrorist incidents were excluded.

Of the 11 preventable deaths (by agreement of three of the five assessors), six patients died from chest injury, two from abdominal trauma, two from head injury and one from hypothermia. Of 15 patients who presented initially to small

Table 1 *Patient details*

Age (years)	
Mean (range)	36 (3–91)
>64*	38 (16)
<15*	30 (13)
Sex ratio (M:F)	194:45 (4·3:1)

*Values in parentheses are percentages

Table 2 *Causes of injury and mortality data in 239 patients*

Cause of injury		No. of deaths
Road traffic accident	110 (46)	33 (30)
Fall	60 (25)	20 (33)
Shooting	23 (10)	12 (52)
Explosion	8 (3)	2 (25)
Burn	8 (3)	1 (12)
Crush	6 (3)	2 (33)
Stabbing	4 (2)	1 (25)
Other assault	3 (1)	0 (0)
Other	17 (7)	3 (18)

Values in parentheses are percentages

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Table 3 *Auditors' assessment of 54 deaths*

Level of agreement	No. of preventable deaths	Median outcome score*	
		Mental	Physical
No. of assessors			
5 of 5	2 (3)	10	8
4 of 5	6 (8)	9	7
3 of 5	11 (15)	8	8

Values in parentheses are percentages. *Prediction of degree of disability using a scale of 0–10

Table 4 *Auditors' recommendations in 54 deaths*

Intervention	No. of times scored
Advanced Trauma Life Support training	40
Consultation with a senior doctor	27
Shorter time to surgery	20
Specialist at hand	12
Better medical management	8
Consultation with intensive care unit	5
Other	6

hospitals and died, only one death was considered preventable. The preventable mortality rate for the large hospitals was 17 per cent (ten of 59). This difference was not significant. The mean age of the 11 patients whose death was preventable was 57 years; two were aged <40 years and five >64 years. Only one had a job at the time of the accident. Two were predicted to have a full mental recovery but none a full physical recovery. Nine of the 11 patients were seen by consultants. In five instances the errors leading to death occurred after 24 h in hospital; these were related to poor management on the ward.

Thirty-nine patients (16 per cent) did not use emergency services to reach hospital. Of those who did, 60 (30 per cent) were >10 min from hospital by road.

In the six small rural hospitals, 14 of 22 patients requiring emergency surgery were seen by a consultant in the accident and emergency department, compared with 18 of 43 in the large hospitals (P not significant). Of the 64 emergency operations, 42 (66 per cent) were performed by consultants, 11 (17 per cent) by senior registrars, eight (12 per cent) by registrars, and in three instances the grade of surgeon was not recorded. In the small hospitals, 11 of 13 emergency operations were performed by consultants. Of 18 patients who required emergency surgery and subsequently died, 14 were operated on by a consultant. The mean time to emergency surgery from arrival in the accident and emergency department was 134 min in the small and 181 min in the large hospitals (excluding patients delayed by computed tomography (CT)) ($P = 0{\cdot}06$).

In all, 121 patients (51 per cent) were transferred to other hospitals, 49 as emergency transfers. Forty-two emergency transfers were for CT (of whom ten required surgery), four were for neurosurgery having already undergone CT and surgery, two for thoracic operations and one for vascular surgery.

Discussion

The key findings of the present study are: the high standard of trauma care in small hospitals; 70 per cent of patients were within 10 min of hospital by road; the relatively low number of patients for the population[3,5], the low number requiring immediate specialist treatment and the large proportion stabilized initially and adequately in small hospitals; the preventable mortality rate was relatively low for a region without centralized trauma services[6]; the mean age of patients with preventable death was 57 years with little impact on regional economic productivity; and the assessors' recommended solutions for errors.

The high standard of care in small hospitals contradicts the usual trend seen in other studies[2,7,8] and the consensus in the literature[5,6,9–11]. This may be due to the high level of consultant involvement and the broad general training of surgeons in Northern Ireland hospitals. The need to bypass hospitals in other systems of trauma care may be because surgeons in these hospitals have a lower exposure to trauma in training (47 per cent see fewer than 20 operative trauma cases[12]) and in practice[13].

In The Royal College of Surgeons of England report[1], only four of 71 patients with trauma were operated on by a consultant surgeon and only 8 per cent of admitted patients saw a consultant on the day of admission.

For paramedics, the maintenance of skills with small numbers of patients will be difficult if a policy of 'scoop and run' within 10 min of hospital is adopted[14]. Given this, and the doubts about the effectiveness of prehospital intravenous therapy[15,16], military antishock trousers[17] and scene delays due to Advanced Life Support procedures[18,19], the role of paramedics in the treatment of these patients is uncertain. In remote areas, advanced prehospital care may be more useful, but skills are harder to maintain.

The small number of patients with trauma in the present study suggests that the large throughput of critical cases per surgeon recommended to develop trauma expertise[3,5] will not be obtained unless surgeons are prepared to work onerous rotas. This volume should fall, reflecting trends in injury mortality rates in Northern Ireland[20]. Although the number of patients with major trauma estimated for the province seems small by some standards (1000 patients per million population[3,5]), it is comparable to other UK figures[21,22], suggesting that surveillance methods were accurate.

Effecting a reduction in the preventable mortality rate may be difficult. A policy of taking patients with trauma to a specialist centre and bypassing small hospitals has reduced the number of preventable deaths in the past[2,8]. The preventable mortality rate in patients who should be taken to a trauma system hospital but are not (one-third of those in a recent study[23]) is unknown. Would the benefits of bypassing hospitals in Northern Ireland outweigh the fall in standards of care in centres excluded from the system, whose staff would rapidly lose their present trauma expertise as a consequence?

Much of the motivation and finance for the restructuring of trauma services came from finding that patients who died from trauma were young wage-earners whose future productivity was lost to society[24,25]. This was not the case in the present study.

There is an 'informal' trauma system in Northern Ireland, with uniform standards of acute care. It can be improved by means of better postgraduate doctor training in trauma and greater access to theatre and senior surgeons. Bypassing the nearest hospital to bring patients in the acute phase to a trauma centre may not be cost–effective or beneficial, and should be contemplated only if the present system fails to improve.

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Announcement

Eurosurgery '93

The 3rd European Congress of Surgery under the auspices of Eurosurgery will take place in London from 14 to 17 September 1993. This international congress embraces all the specialties within surgery and sessions will be sponsored by all of the surgical specialist associations and societies of the participating nations, ensuring that there will be an international and multidisciplinary approach to many common surgical problems. Additionally, there will be European symposia of general interest to all surgeons on themes such as endoscopy, management of patients with trauma, daycase surgery, graduated patient care, surgical audit and surgery in the developing world. A major session on surgical training is also being organized by the surgical trainees' associations.

A large number of free papers will also be given and these communications will be published in a special supplement of *The British Journal of Surgery*.

On 14 September 1993 a number of satellite sessions sponsored by companies are being organized for delegates.

Further details and registration forms may be obtained from the Congress Secretariat, Eurosurgery 1993, Conference Associates and Services Ltd, Congress House, 55 New Cavendish Street, London W1M 8RE, UK. Telephone: 071 436 0531. Facsimile: 071 935 7559.

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Prognostic signs in the evaluation of patients with minor head injury

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To assess signs that might be used in the decision whether or not to admit a patient with minor head injury, the records of 713 female and 1163 male patients were reviewed. Skull radiographs were not obtained routinely; all patients were able to walk and talk when they reached medical contact. Nine patients developed an intracranial complication. The risk of developing such a complication was 16·7 per cent when the patient was agitated, 3·4 per cent in the presence of impaired consciousness and 2·1 per cent when positive neurological signs were observed at the time of examination. Based on the medical history, amnesia for >5 min and vomiting were associated with a risk of 3·3 and 1·2 per cent respectively; the risk increased considerably in the presence of both. It is recommended that all patients presenting themselves with one or more of the above symptoms or signs, or with alcohol intoxication, after a minor head injury be admitted for observation. If these guidelines had been used, all patients with an intracranial complication would have been detected, and 44·5 per cent of the bed-days used would have been saved.

Minor head injury is common in modern society. Carlsson[1] found an incidence of up to 5000 per 100 000 population per year in a Swedish study. Some patients are admitted for observation in case an intracranial complication develops. In Denmark, the diagnosis of cerebral concussion (International Classification of Diseases no. 850) is the seventh most common reason for hospital admission; the incidence of admission[2] is 286 per 100 000 population per year. These patients represent a heavy burden on the healthcare system and a safe reduction in the number of admissions would be desirable.

Symptoms such as brief unconsciousness and amnesia, vomiting and headache after a minor head injury have for many years been a sufficient basis for admitting patients for observation, but this policy has led to an excessive number of precautionary admissions[3]. Several studies[4–9] have promoted guidelines to be used in the decision to admit or send home patients presenting to the accident and emergency department with a minor head injury. Some studies[5,7–9] have advocated the use of skull radiography in the decision-making process but the present authors have not used this investigation routinely in the evaluation of patients with minor head injury.

The purpose of the present study was to assess which clinical characteristics might be used as prognostic features by the accident and emergency doctor when deciding whether or not to admit a patient for observation after a minor head injury. A calculation of the risk of developing an intracranial complication when these features are present has been made and the potential economic savings of using these features in the admission strategy have been assessed.

Patients and methods

The records of 713 female and 1163 male patients of mean(s.d.) age 27·5(19·9) years admitted after a minor head injury between 1 January 1985 and 31 December 1986 were reviewed. The only indication for admission was to allow observation for development of an intracranial complication. Such a complication could be one of several intracranial lesions, such as a haematoma or contusion. Criteria for admission included the presence of one or more features such as headache, vomiting, brief amnesia and/or unconsciousness, agitation (defined as unusually troubled behaviour), impaired consciousness at the time of examination, an abnormal neurological sign found at the examination, difficulty in assessing the patient because of alcohol intoxication, epilepsy or other serious medical condition, and suspicion of a skull fracture. All patients were able to walk and talk when they reached medical contact. Patients with depresssed or basilar fractures and compound head injury were excluded.

Patients were seen in the accident and emergency department by a junior doctor who decided whether to admit or send home. Skull radiography was obtained only when considered necessary by the examining doctor. Patients were admitted to the neurosurgical, orthopaedic or paediatric department according to a predetermined schedule.

Those who deteriorated were seen by an experienced neurosurgeon who decided whether or not to perform computed tomography (CT). Only patients who were in a clinical state such that the neurosurgeon believed them likely to have an intracranial complication underwent CT.

To determine whether any of the factors shown in *Table 1* was a better predictor of deterioration than CT, multiple logistic regression analysis was carried out. The significant variables were selected by a stepwise procedure. The model was tested for interaction between the variables to determine whether any might act as a confounder. CT was used as the dependent variable and all the variables shown in *Table 1* were treated as independent variables. A significance level of 5 per cent was used. On the basis of this calculation, odds ratios for the significant variables were computed.

The risk of developing an intracranial complication (positive predictive value) when presenting with one of the symptoms, as well as the 95 per cent confidence interval, was calculated from the observed frequencies. The value was estimated as the ratio between the number of patients who exhibited the symptom and later developed an intracranial complication and all those who exhibited the symptom.

Results

A total of 27 patients underwent CT. Nine patients developed an intracranial complication (*Table 2*); three of these had surgery and one died (all received CT). In *Table 1* epidemiological data, the number of CT investigations carried out in each subgroup and the significance level resulting from multiple regression analysis are shown. Despite the fact that the number of CT scans was relatively low, significant results were revealed. No interaction between the variables could be demonstrated; even though children accounted for almost one-third of the population, this was not a confounding factor.

Table 3 shows the significant variables and the odds ratio for developing a condition for which skilled neurosurgeons would expect the patient to have an intracranial complication and therefore order CT. *Table 4* shows the risk and the

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Table 1 *Epidemiological data, symptoms in the medical history and signs observed by the doctor at the time of examination in the accident and emergency department used as independent variables in logistic regression analysis*

Data no.	Variable	No. of patients ($n = 1876$)	No. of CT investigations	P
Epidemiological				
1	Sex			
	F	713 (38·0)	10	n.s.
	M	1163 (62·0)	17	
2	Cause of minor head injury			
	Accident at home	325 (17·3)	7	n.s.
	Accident at work	81 (4·3)	3	
	Traffic	638 (34·0)	9	
	Sport	187 (10·0)	3	
	Assault	346 (18·4)	1	
	Other	299 (15·9)	4	
3	Trauma			
	Trivial	616 (32·8)	7	n.s.
	Moderate	1113 (59·3)	12	
	Severe	147 (7·8)	8	
4	Age (years)			
	0–14	595 (31·7)	6	n.s.
	15–29	532 (28·4)	8	
	30–44	385 (20·5)	4	
	≥45	364 (19·4)	9	
Medical history				
5	Amnesia			
	None	1001 (53·4)	6	0·007
	≤5 min	721 (38·4)	12	
	>5 min	154 (8·2)	9	
6	Unconsciousness			
	None	1035 (55·2)	12	n.s.
	≤10 min	813 (43·3)	14	
	>10 min	28 (1·5)	1	
7	Headache			
	None	778 (41·5)	7	n.s.
	Moderate	941 (50·2)	15	
	Heavy	157 (8·4)	5	
8	Vomiting			
	No	1363 (72·7)	11	0·005
	Yes	513 (27·3)	16	
9	Convulsions			
	No	1854 (98·8)	25	n.s.
	Yes	22 (1·2)	2	
10	Dizziness			
	No	1524 (81·2)	25	n.s.
	Yes	352 (18·8)	2	
Examination				
11	Alcohol intoxication			
	None	1338 (71·3)	20	n.s.
	Moderate	272 (14·5)	3	
	Massive	266 (14·2)	4	
12	Consciousness level			
	Alert	1629 (86·8)	11	0·0002
	Impaired	237 (12·6)	14	
	Unconscious	10 (0·5)	2	
13	Agitation			
	No	1858 (99·0)	23	0·01
	Yes	18 (1·0)	4	
14	Pupils			
	Uniform	1771 (94·4)	25	n.s.
	Different	105 (5·6)	2	
15	Neurological signs			
	None	1828 (97·4)	22	0·009
	Positive	48 (2·6)	5	

Values in parentheses are percentages. CT, computed tomography; n.s., not significant

95 per cent confidence interval for developing an intracranial complication calculated from the observed frequencies in the present series. The risk of developing a complication increased considerably when patients exhibited two of the significant symptoms (*Table 5*).

To test the statistical findings, the symptoms outlined in *Table 4*, with a risk of complication of 1 per cent or more, were applied to the material as guidelines. If these guidelines had been used for the present patients, 834 would have been admitted to hospital. Alcohol intoxication may impede the evaluation of patients with minor head injury[10]; in the present series 42·0 per cent of adults were intoxicated. Accordingly, all patients with this condition who had not already been incorporated were also included. Following this procedure, a total of 963 of the 1876 patients would have been admitted. All those who developed an intracranial complication were in this

Table 2 *Intracranial complications shown by computed tomography*

Lesion	No. of patients
Subdural haematoma	1
Traumatic subarachnoid haematoma	1
Intracerebral haematoma	4
Diffuse cerebral contusion	3
Total	9

Table 3 *Odds ratios for the variables identified as significant in computed tomography analysis* (Table 1)

Data no.	Variable	Odds ratio for computed tomography
5	Amnesia	
	None	1·0
	≤5 min	2·9
	>5 min	6·4
8	Vomiting	
	No	1·0
	Yes	3·4
12	Consciousness level	
	Alert	1·0
	Impaired	5·1
	Unconscious	14·0
13	Agitation	
	No	1·0
	Yes	6·6
15	Neurological signs	
	None	1·0
	Positive	5·6

Table 4 *Risk* (*positive predictive value*) *of developing an intracranial complication calculated from observed frequencies* (n = *1876*) (Table 1)

Data no.	Variable	Risk (95% confidence interval) of intracranial complication (%)
5	Amnesia	
	None	0·0 (0·0–0·4)
	≤5 min	0·6 (0·2–1·4)
	>5 min	3·3 (1·1–7·4)
8	Vomiting	
	No	0·2 (0·0–0·6)
	Yes	1·2 (0·4–2·5)
12	Consciousness level	
	Alert	0·06 (0·0–0·4)
	Impaired	3·4 (1·5–6·5)
	Unconscious*	—
13	Agitation	
	No	0·3 (0·1–0·9)
	Yes	16·7 (3·6–41·4)
15	Neurological signs	
	None	0·4 (0·1–1·1)
	Positive	2·1 (0·1–11·1)

*No patients were unconscious and developed an intracranial complication

Table 5 *Risk (positive predictive value) of developing an intracranial complication when exhibiting two significant symptoms or signs, calculated from observed frequencies* (n = *1876*)

	Amnesia >5 min	Vomiting	Impaired consciousness	Agitation	Neurological signs
Amnesia >5 min	—	12·1	9·5	60·0	16·6
Vomiting		—	7·7	33·0	5·9
Impaired consciousness			—	—	11·1
Agitation				—	50·0
Neurological signs					—

Values are percentages

group. In total, 284 patients underwent skull radiography. In 25, the radiograph demonstrated a fracture; one of these patients had an intracranial complication. This patient already had severe amnesia, impaired consciousness and vomiting on arrival at the accident and emergency department. Two patients with negative skull radiography developed an intracranial complication.

Admissions accounted for a total of 3330 bed-days. By using the above guidelines 1481 bed-days (44·5 per cent) would have been saved. The bed-day expenditure covering the entire nation with a population of approximately 5 million for patients with minor head injury was £5 400 000 in 1985[11]. The total savings in Denmark would thus amount to approximately £2 400 000 (at the 1985 level).

Discussion

Patients with minor head injury represent a common problem in the accident and emergency department. The present group of patients comprised 5 per cent of all those admitted as emergencies to this hospital[2]. The essential difficulty is to discern between patients who will develop an intracranial complication and those who will not[12]. Generally, around 20 per cent of adult attenders and 10 per cent of children are admitted[12]. A considerable proportion are admitted 'just in case', presumably because accident and emergency doctors are uncertain in their judgement. Less than 1 per cent of patients with a minor head injury will develop an intracranial complication[13]. In the present study, the incidence was 0·5 per cent, which is similar to the level reported by Jones and Jeffreys[14] from 16 general hospitals and by Miller and Jones[7] from a head injury unit, but less than the 3 per cent of Dacey *et al.*[15] in a neurosurgical department (this is caused partly by the inclusion of some patients with compound depressed skull fractures).

In an attempt to identify safe prognostic factors, the present authors used deterioration to such an extent that an experienced neurosurgeon would refer the patient for CT as the 'gold standard'. Two symptoms from the medical history, amnesia for >5 min and vomiting, were significant; furthermore, alteration in the level of consciousness and positive neurological signs were associated with a high risk of deterioration. The characteristics delineated in the present study conform almost exactly to those found by Weston[8] and Miller and Jones[7].

Having identified the above characteristics, the risk (positive predictive value) of developing an intracranial complication was computed, when presenting with the symptoms. The most important characteristic was either agitation or depressed consciousness at examination in the accident and emergency department, followed by amnesia for >5 min. The risk of developing a complication increased considerably when the patient presented with two of the significant variables, reaching 60·0 per cent for presentation with both amnesia for >5 min and agitation.

Several of the conventional features of concussion, such as headache, convulsions, dizziness and unconsciousness in the history, trauma severity and age, did not influence the outcome after minor head injury, provided that the patient was able to walk and talk on arrival at hospital. It is well known that alcohol intoxication may interfere with the evaluation, especially assessment of the level of consciousness[10]. Even though alcohol intoxication was not significant, for medicolegal reasons the authors recommend that all patients exhibiting such intoxication, if it interferes with assessment, be admitted.

Many doctors in accident and emergency departments are inexperienced, and the use of better defined guidelines for admission can reduce the number of patients hospitalized. If the guidelines shown below had been used on the present patients, the number of admissions would have been reduced by 48·7 per cent and the number of bed-days by 44·5 per cent; all patients who later developed an intracranial complication would still have been admitted. These figures, which correspond to earlier results[8] are, of course, calculated on a theoretical basis. Experience with implementation of guidelines suggests that 100 per cent compliance is illusory[16]. On the other hand, guidelines usually increase clinicians' awareness, leading to a reduction in the use of resources[4]. This study was not designed to account for patients who were discharged from the accident and emergency department.

The authors advocate that patients who exhibit one or more of the symptoms listed below after a minor head injury be admitted for observation:

1. Agitation, defined as any troubled behaviour at examination.
2. Impaired consciousness or coma at the time of examination.
3. Positive neurological signs.
4. Amnesia for >5 min.
5. Vomiting.
6. Alcohol intoxication that interferes with the assessment.

The economic impact of this group of patients is large[13]. In 1985, the mean expenditure in Denmark for identifying one patient with an intracranial complication was around £80 000; the mean expenditure for identifying one patient who needed surgery[11] was £180 000. With a population of 5 million, patients admitted with the diagnosis of concussion accounted for a total expenditure[11] of around £5 400 000. The potential savings using the above guidelines would amount to £2 400 000 per year (at the 1985 level).

In the search for better means of predicting which patients will develop a complication, British neurosurgeons[5,9,17–21] in particular have advocated the routine use of skull radiography. In the authors' departments, the regular use of skull radiography was abandoned after the report from The Royal College of Radiologists[22]; skull radiology is now used only for specific indications. Consequently, the present patients were admitted only on the basis of medical history and clinical evaluation in the accident and emergency department. In all, 15·1 per cent of patients underwent skull radiography; one of 25 with a fracture developed an intracranial complication. This patient already demonstrated positive characteristics according to the guidelines on arrival at hospital, and would therefore have been admitted irrespective of the finding of skull fracture.

The risk of developing intracranial haematoma has been estimated to be increased 200-fold if a fracture is present[23]. The absolute risk of developing an intracranial haematoma in the presence of a skull fracture has been shown to be 1 in 32 if the patient is orientated and 1 in 4 if disorientated[20]. These figures have been confirmed by Teasdale *et al.*[9]. Both of these studies[9,20] included patients with severe head trauma, as well as those with minor injuries. In the present study only patients who were able to walk and talk were evaluated, because they represent the real clinical problem for the accident and emergency doctor. The finding of a skull fracture has been suggested as the only factor than can distinguish the at-risk group of patients among those with no obvious features in the history or neurological signs[14]. However, except for the use of the Glasgow Coma Scale, which was not intended as a means of distinguishing between patients with minor head injury[13], the above study[24] did not incorporate the two descriptive signs (agitation and impairment of consciousness without coma) that were found to be the most important factors in the present study.

These and other studies[15,17,19] focus on the presence of skull fracture and perhaps one or two clinical features. None of these studies has considered all the clinical aspects in patients with a minor head injury (unlike the present study) and related them to intracranial complication as the endpoint. While the conclusions of such studies are not wrong, they conceal a relevant clinical possibility, namely that the clinical outcome, in patients with minor head injury, might have been predicted from the history and clinical examination alone. Other studies have found routine skull radiography to be unnecessary in the evaluation of patients with minor head injury[4,6,22,25–27] and an editorial[28] in the *Lancet* in 1987 supported that view. We agree that skull radiography adds no further information to the decision whether to admit or send home patients with a minor head injury.

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Plantar melanoma in black South Africans

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The outcome of treatment in 40 black patients (27 women, 13 men; mean age 62·9 years) with plantar melanoma over a 13-year period was analysed to evaluate the efficacy of wide local excision with split skin grafting. Substantial delay in seeking medical attention occurred in 35 patients. At presentation, 20 patients had stage I disease, one stage II, 15 stage III and four stage IV. Acral lentiginous melanoma (27 patients) was the most common histological type. The mean Breslow depth was 6·9 mm and 35 patients had lesions of Clark level IV or V. The mean surface area of plantar lesions was 13·3 cm². Wide local excision with split skin grafting was used in 29 patients; four patients with neglected advanced plantar lesions had below-knee amputation and seven with metastatic disease did not undergo surgery. Graft sepsis occurred in six patients and local recurrence in two. Nine patients were alive at follow-up; the 5-year survival rate was 25 per cent. Delay in presentation and locally advanced disease may explain the poor prognosis of plantar melanoma in black South Africans.

The volar skin and nailbed are infrequent sites of malignant melanoma in Caucasians[1–3] but there is variation in the incidence and regional distribution of malignant melanoma in different ethnic groups[2,4–6]. The volar–subungual area is the most common site of malignant melanoma in Japanese[7], Chinese[8], Puerto Rican[9] and black[10] populations. Acral melanomas are often grouped with other melanomas of the extremities or those arising on the dorsal aspect of the hand or foot. There is evidence, however, that plantar melanoma is a distinct entity with special clinical and pathological characteristics[1,11–13]. The prognosis for patients with plantar melanoma is worse than that for melanoma in other locations[6,14]. The diagnosis is often delayed[2,14,15] and plantar lesions are frequently advanced at presentation with ulceration, necrosis and bleeding[2,3,12].

The management of plantar melanoma is demanding to obtain control of local disease and rehabilitation of the patient. The requirements are a durable and functional weight-bearing surface[16] while satisfying oncological principles in patients with advanced disease. This study analysed the results of treatment of plantar melanoma in 40 consecutive black patients over a 13-year period.

Patients and methods

The records of 1420 patients registered at the Melanoma Clinic, Groote Schuur Hospital, Cape Town, between 1972 and 1985 were reviewed. During this period 63 black patients were seen, 40 of whom had melanoma involving the sole of the foot. Clinical data included patient characteristics, duration of disease before diagnosis, stage at presentation, tumour site, surgical treatment of the primary lesion and subsequent clinical course. Histological review of the primary lesion included histogenetic subtype, Breslow thickness and Clark level of penetration. The surface area of the lesion was calculated after measuring the dimensions of the excised pathological specimen.

Operation

Most plantar melanomas were cleared with a 3-cm margin with excision down to the heel fat pad, small muscles or plantar fascia of the sole of the foot. Excision margins were reduced to 2 cm in some lesions to avoid functional impairment and preserve the residual plantar weight-bearing surface. Defects were closed with a primary split skin graft. In those with non-salvageable advanced tumours, primary amputation was performed. Therapeutic nodal dissection was carried out for metastatic regional lymphadenopathy. Patients with metastatic disease not amenable to surgical resection were treated with multiagent chemotherapy. The survival times for all patients were measured from the date on which the diagnosis of malignant melanoma was first established from biopsy material to the time of death or the termination of the study.

Results

The 40 patients comprised 27 women and 13 men with a mean age of 62·9 (range 30–83) years at presentation. Substantial delay (mean 20 months (range 2 months to 14 years)) occurred in 35 patients before medical attention was sought. Twenty patients had stage I disease on presentation, one stage II, 15 stage III and four stage IV. The heel was involved in 26 patients, the ball of the foot in ten and the arch in four (*Figure 1*). The lesion was ulcerating in nine patients and fungating in 11. The most common histogenetic type was acral lengitinous melanoma (27 patients). Nodular melanoma occurred in eight patients, superficial spreading melanoma in two and three lesions were unclassifiable. The mean Breslow depth of penetration was 6·9 (range 1·5–25) mm. Clark level V lesions were present in 20 patients, level IV in 15, level III in one and could not accurately be determined in four. The mean surface area of all plantar lesions was 13·3 cm².

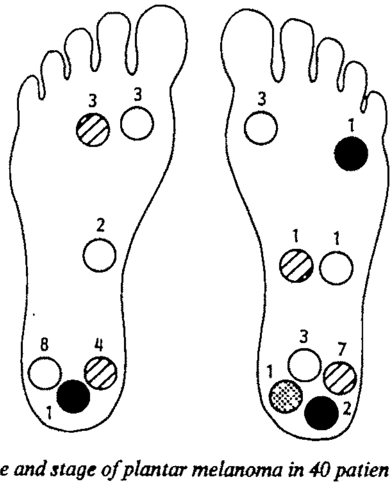

Figure 1 *Site and stage of plantar melanoma in 40 patients.* ○, *Stage I;* ◍, *stage II;* ⊘, *stage III;* ●, *stage IV*

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In the 20 patients with stage I disease, the heel was the most common site of involvement (11 patients), followed by the forefoot (six) and the plantar arch (three). The mean Breslow depth of penetration was 6·2 (range 1·5–11·5) mm. Seven patients had Clark level V lesions, 11 level IV and one level III; in one patient the level could not be accurately determined. Eighteen patients underwent wide local excision and split skin grafting. The mean surface area of the defect after wide excision was 31·7 (range 13·6–36·7) cm^2. Local sepsis occurred in three patients with loss of the graft; all three subsequently required regrafting. Four patients had incomplete take of the graft and one developed a keloid of the split skin graft. Two patients underwent below-knee amputation as the primary procedure because of the extent of disease on the heel. Six patients underwent isolated hyperthermic limb perfusion, two after below-knee amputation and four in addition to wide local excision and skin grafting. One patient underwent prophylactic block dissection in addition to wide local excision and skin grafting. Two patients with deep lesions developed local recurrence in the graft site. One developed systemic disease and has died; the other is well 5 years after below-knee amputation. Six patients subsequently underwent therapeutic inguinal node dissection, one of whom is alive at 62 months; five developed systemic disease and died. Two patients have been lost to follow-up at 3 and 6 months. Eight patients with stage I disease (mean Breslow depth 3·9 mm) are alive at a mean follow-up of 46 (range 13–156) months and ten (mean Breslow depth 7·1 mm) have died.

One patient presented with stage II disease involving the heel and had a below-knee amputation because of extensive local disease. He subsequently underwent therapeutic regional lymph node dissection and died 36 months after presentation.

Fifteen patients presented with stage III disease. The heel was the most common site, being involved in 11 patients (*Figure 1*). The mean Breslow depth was 7·9 (range 3·7–25) mm. Eleven patients underwent wide local excision, split skin grafting and therapeutic lymphadenectomy. Sepsis occurred in three patients and regrafting had to be performed. Three subsequently had limb perfusion. One patient underwent below-knee amputation and lymph node dissection. Two patients refused all treatment. One patient with advanced local disease declined amputation and was treated with radiotherapy and chemotherapy. One patient was lost to follow-up at 4 months; one is known to be well after 38 months. Thirteen patients died at a mean of 15 (range 3–34) months from metastatic disease.

Four patients presented with stage IV disease and all have died after a mean of 3·5 (range 3–5) months.

Discussion

Malignant melanoma is uncommon in the indigenous South African population[17,18], with a reported incidence[19] of approximately 1 in 100000. Giraud *et al.*[18] reported that 80·4 per cent of melanomas in black South Africans occurred in the lower extremity, and Isaacson *et al.*[10] in a series of 83 patients found that 70 lesions arose on the foot. The propensity for melanoma in black patients to occur on volar and plantar surfaces is well established but no aetiological significance has been attributed to this observation[13].

Acral lentiginous melanoma was the most common histogenetic type and occurred in 68 per cent of the present patients. Feibleman *et al.*[12] reported that the majority of acral lentiginous melanomas occur on the foot and most frequently in weight-bearing areas. Slingluff *et al.*[20] found that acral lentiginous melanoma had a strong ethnic predilection and that most patients with plantar melanoma of this type were black. Fungation, ulceration, necrosis and bleeding were common in patients in the present study. The high incidence of regressive changes and desmoplasia in acral lentiginous melanoma[3], together with the thickness and unique microanatomy of the skin of the sole, make accurate determination of the interface between papillary and reticular dermis difficult[1]. Assessment of Clark level, using microanatomical landmarks, is often subjective, particularly in differentiating level III from level IV lesions[12]. The Breslow depth of penetration measured by ocular micrometry may be skewed by the thickness of the overlying epidermis. Despite these histological constraints, determination of Clark level and measurement of depth of invasion remain the most useful indicators of prognosis[3].

Wide local excision is the standard method of treatment for plantar melanoma[21]. A considerable portion of the plantar surface had to be excised to obtain adequate local clearance in the present study; the area of the resulting defect was similar to the 29·7 cm^2 reported by Wottering *et al.*[22]. Reconstruction of large plantar defects, particularly those involving the weight-bearing sole and heel, is often difficult because of the unique anatomical characteristics adapted to withstand pressure and shearing forces[23]. Where possible sufficient plantar surface for weight bearing was maintained. Balch[21] similarly advocated retaining a portion of the heel or ball to bear pressure during walking and recommended preservation of the deep fascia on the flexor tendons as a base for skin coverage. Patients in the present study were routinely given polyethylene shoe inserts to reduce pressure on the graft site and decrease shear forces. Despite the use of modified footwear with functional padding, hyperkeratosis of the graft and fissuring of adjacent pressure-bearing areas occurred in some patients. Regular physiotherapy and careful rehabilitation overcame most disabilities and provided a satisfactory result.

Survival of patients with acral melanoma is primarily a function of the same variables important in other types of melanoma. Increased risk for plantar melanoma is associated with Clark level IV or V, Breslow depth >2·25 mm and stage of disease[24]. Multivariate analysis for stage I acral melanoma found that three prognostic variables – ethnic group, ulceration of the primary lesion and Clark level – were significant for prediction of both disease-free interval and survival rate[20]. Melanoma in the black South African population has an aggressive course. Giraud *et al.*[18] cited a 5-year survival rate of 19·6 per cent compared with 25 per cent in the present study. In a North American series[6], black patients had a poorer prognosis than the white population, which could not be explained by more advanced Clark level, greater age or worse stage of disease at presentation. The mean thickness of plantar melanoma in the present group of patients was 6·9 mm, which is considerably deeper than values in previous reports. The high incidence of regional and systemic metastases at presentation and after excision of the primary tumour suggests that these lesions have often advanced beyond the local site at the time of diagnosis. Paladugu *et al.*[3] reported that the mortality rate was proportional to the depth of penetration and this fact, together with delayed presentation and advanced disease, may explain the poor prognosis in the present patients.

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Announcement

The Melanoma Study Group and British Association of Plastic Surgeons randomized controlled trial of excision width of cutaneous malignant melanoma of depth ≥2 mm

Does a greater width of excision of malignant melanoma confer benefits in terms of lower local and metastatic recurrence rate? A 1-cm excision can generally be performed under local anaesthesia as an outpatient procedure with primary skin closure whereas a 3-cm margin may require general anaesthesia, inpatient care and skin grafting or other means of reconstruction.

To address such issues, The Melanoma Study Group and British Association of Plastic Surgeons are undertaking a randomized controlled trial of 1-cm *versus* 3-cm excision margins for cutaneous malignant melanoma of depth ≥2 mm. The trial aims to assess the effect of excision margin on local and in-transit recurrence, regional lymph node and distant metastasis, and patient survival.

To be eligible, patients must have primary single localized malignant melanoma of depth ≥2 mm not of the head or neck, fingers, toes, soles of the feet or palms of the hand. They must be over 18 years of age, not pregnant if female, consent to the study and be available for follow-up. Patients must have no previous history of cancer and not be receiving immunosuppressive or adjuvant therapy.

Tumours of this depth are uncommon; an individual surgeon may see no more than two or three per year. Surgeons who do not see many melanomas may still make an invaluable contribution; all are invited to join the study. For further information and a copy of the protocol please contact: Mr J. Meirion Thomas, Consultant Surgeon, Royal Marsden Hospital, Fulham Road, London SW3 6JJ. Telephone: 071 352 2269. Facsimile: 071 259 9552.

J. Meirion Thomas
Chairman of Working Party

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Low-dose tumour necrosis factor α and melphalan in hyperthermic isolated limb perfusion

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Nine patients with soft tissue tumours of the lower limb not amenable to treatment other than by isolated limb perfusion or amputation underwent hyperthermic isolated limb perfusion at the level of the superficial femoral vessels, using a combination of recombinant tumour necrosis factor (TNF) α and melphalan. In seven patients with superficial tumours, necrosis and sloughing was apparent within 48 h of perfusion. All patients experienced a complete tumour response. There were no systemic side-effects associated with the use of TNF-α although local side-effects, particularly oedema, were pronounced. Three patients ultimately required amputation because of the large soft tissue defects that resulted from necrosis of the tumour and overlying skin.

Hyperthermic isolated limb perfusion with melphalan is well established as a palliative treatment for malignant melanoma[1,2]. To a lesser extent the technique has also been used in the treatment of soft tissue sarcoma and squamous cell carcinoma[3]. Nevertheless, isolated limb perfusion with melphalan is not an attractive surgical option, being a major procedure with an appreciable morbidity rate and with response rates and duration that are unpredictable but often unsatisfactory[2].

Experimental evidence suggests a synergistic effect between tumour necrosis factor (TNF) and various cytotoxic agents including melphalan[4]. The antitumour activity of TNF can be further enhanced by interferon (IFN) γ, which induces an increase in the number of cell-surface receptors for the cytokine[5]. These experimental observations have been applied in a recently published series of patients treated by isolated limb perfusion with a combination of recombinant human tumour necrosis factor (rTNF) α, IFN and melphalan[6]. A relatively high dose (2–4 mg) of rTNF-α was used, and most perfusions were performed through the iliac vessels. The level of perfusion is important, because isolating the system becomes progressively more difficult at proximal sites and the consequent risk of cytotoxic substances leaking into the systemic circulation increases. All patients in the high-dose TNF series[6] experienced postoperative pyrexia, and two (9 per cent) suffered severe systemic toxicity with circulatory shock. Furthermore, the risk of systemic side-effects was considered high enough for all patients to be monitored in the intensive care unit and to be hyperhydrated and given prophylactic continuous infusion of dopamine before and for at least 72 h after injection of rTNF-α.

The results are reported of a pilot study using a low dose of rTNF-α with melphalan in hyperthermic isolated perfusion through the superficial femoral vessels.

Patients and methods

Nine patients were treated between July 1991 and February 1992 (*Table 1*). They were selected for treatment because they had locally advanced bulky tumours. The patients with melanoma could have been treated with melphalan alone, although in patients 2 and 3 disease was so extensive and bulky that amputation would also have been a reasonable option. The four patients with soft tissue sarcoma were selected for treatment by isolated limb perfusion because the position of the tumour (encasing the ankle joint in patient 8, involving the knee joint in patient 9) or extent of the lesion (patients 4 and 7) made them unsuitable for wide excision and radiotherapy. The first patient in the series had developed extensive local recurrence of a squamous cell carcinoma after previous operation and had been offered above-knee amputation elsewhere. The selection of patients was limited to those with locally advanced disease, in whom amputation would otherwise be an acceptable option, because of the local toxicity that might result from the therapy.

Before undergoing treatment with rTNF-α, all patients had the operation of isolated limb perfusion fully explained to them. The experimental nature of treatment with rTNF-α was stressed, including the possible risk of ultimate amputation. In addition to the verbal explanation, patients were given a printed information sheet. The standard hospital consent form was signed with additional consent relating to the use of rTNF-α.

Reports from phase 1 studies suggested that the systemic effects of rTNF-α could be reduced by prophylactic administration of steroids and non-steroidal drugs[7,8]. Despite their lack of proven efficacy in this regard, it was considered prudent to give a single perioperative dose of each. Premedication with pethidine and atropine was accompanied by diclofenac 100 mg 1 h before surgery. Anaesthesia was induced with thiopentone and fentanyl, after which the patient was paralysed with vecuronium and intubated. Maintenance of anaesthesia was with nitrous oxide, oxygen and isoflurane. After induction a radial artery line, triple-lumen central venous catheter and pulmonary artery line were inserted. The patients were haemodynamically monitored throughout the procedure.

With a 10-cm high-thigh tourniquet in place and after administration of heparin, the superficial femoral vessels were cannulated as far proximal as possible in Hunter's canal to establish an extracorporeal circulation. At a tourniquet pressure of 300 mmHg, perfusion was started with 250 ml packed cells and 500 ml Hartmann's solution. The limb was warmed via the extracorporeal system with a pump flow of around 350 ml/min, temperature being monitored by a subcutaneous needle thermocouple in the foot. Melphalan was given via the extracorporeal pump as a bolus (1·5 mg per kg body-weight) and circulated for 15 min, after which a bolus dose of rTNF-α was administered (500, 250 and 125 μg for patients 1–5, 6 and 7, and 8 and 9 respectively). Both drugs subsequently circulated for 30 min at a flow rate of 250–300 ml/min and a foot skin temperature of 38°C. Methylprednisolone 2 g was given systemically before injection of rTNF-α. After drug circulation, the system was washed out with 1000 ml Hartmann's solution. The circuit was then reprimed with 250 ml packed cells and 500 ml Hartmann's solution, and the system was perfused for a further 15 min. A second washout with 2000 ml Hartmann's solution preceded cessation of the isolated perfusion and deflation of the tourniquet. After removal of the cannulas, the femoral vessels were repaired with 5/0 nylon sutures and the thigh wound was closed in routine fashion. Patients 8 and 9 underwent medial and lateral fasciotomy to decompress the muscle compartments of the lower leg. After operation patients were transferred to the intensive care unit for overnight observation.

Blood samples were taken throughout the procedure from the perfusate and from the radial and pulmonary arteries to monitor levels of rTNF-α. Measurement was performed using an enzyme-linked immunosorbent assay (National Institute for Biological Standards and Controls, Hampstead, UK) standardized against rTNF-α 87/650 with a between-batch coefficient of variation below 15 per cent and a measuring range of 15–1000 units/ml.

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Table 1 *Details of patients*

Patient no.	Age (years)	Sex	Pathology*	Site	Previous treatment
1	50	F	Squamous cell carcinoma (20 × 10 cm)	Invading anterior surface of tibia	Local excision and skin graft
2	70	F	Melanoma stage IIIA with 6 × 5 cm fungating lesion	Ankle	Local excision, carbon dioxide laser ablation
3	50	F	Melanoma stage IV with 7 × 9 cm and 6 × 7 cm fungating lesions	Calf	Wide excision and skin graft, isolated limb perfusion, chemotherapy
4	61	M	High-grade soft tissue sarcoma	Anterior leg invading tibia and skin	Radiotherapy
5	79	F	Melanoma stage IIIA	Leg	Wide excision, carbon dioxide laser ablation
6	62	F	Melanoma stage IIIA	Leg	Wide excision and skin graft
7	43	M	High-grade soft tissue sarcoma	Leg invading skin	Inadequate surgery
8	41	M	High-grade soft tissue sarcoma	Encasing ankle	Biopsy
9	22	F	High-grade soft tissue sarcoma	Knee joint	Biopsy

*Staging follows the M. D. Anderson Cancer Center classification

Results

All patients were alive at a median follow-up of 11 (range 5–13) months after limb perfusion.

The seven patients in whom the lesion was visible and palpable showed tumour softening and necrosis within 48 h of perfusion. Loss of uninvolved skin overlying the tumour and subsequent impaired healing occurred in three patients: in nos 4 and 5 intact skin necrosed in the immediate postoperative period, and in patient 1, in whom there was preoperative skin breakdown, healing had not occurred after 13 months. Where the tumour volume was very large, necrosis resulted in tissue defects that required debridement; a free latissimus dorsi myocutaneous flap was required for reconstruction in patient 7.

Severe oedema developed in the perfused limb within 24 h of operation in patients 1–7. The oedema persisted despite elevation and was accompanied by joint stiffness requiring physiotherapy. Presumably as a consequence of oedema causing increased intracompartmental pressure, all patients developed neuropathy with reduced skin sensation over the foot and lower leg. This neuropathy gradually improved except in patients 1–3, in whom loss of sensation was accompanied by foot drop. To avoid these sequelae of postoperative oedema, medial and lateral fasciotomy was performed in patients 8 and 9. For the same reason the dose of rTNF-α was reduced as the series progressed.

All patients had a complete response to treatment. In patients 1–7, who had superficial disease, response was proven by biopsy. Patients 8 and 9 had periarticular disease; computed tomography and fine-needle aspiration biopsy 8 weeks after operation showed no evidence of viable tumour. There has been no tumour recurrence in the treated limbs during follow-up.

Large soft tissue defects that did not heal followed tumour necrosis in patients 2–4. For example, in patient 3 a cavity extended through the calf muscles following the disappearance of large deep tumour deposits from the medial and lateral aspects of the leg. Above-knee amputation had to be performed in these three patients 11–12 weeks after perfusion. Examination of the amputation specimens showed no evidence of residual tumour.

The first patient in the series was the only one to experience systemic leakage of rTNF-α (details have been described previously[9]), and neither she nor any other patient suffered from systemic side-effects. In patient 1 systemic arterial levels (radial artery) of rTNF-α did not rise above 0·425 ng/ml (17 units/ml), while the mixed venous concentration (pulmonary artery) increased within 10 min of injection to peak at 1·855 ng/ml (74 units/ml) after 30 min. The venous half-life of rTNF-α was 17 min. The concentration of rTNF-α in the perfusate was measured in all patients, and levels of 0·50–0·75 μg/ml (20 000–30 000 units/ml) were reached in the circulating fluid.

Discussion

Locally and systemically administered TNF-α has been shown to produce malignant cell death and haemorrhagic necrosis of tumours[4]. However, phase 1 studies using systemic rTNF-α reported severe side-effects that limited the maximum tolerated dose, resulting in lower drug concentrations than those associated with tumour response in animals[7,8]. None of the published phase 1 studies has demonstrated a convincing anticancer effect. In principle, isolated limb perfusion is an ideal method of administering TNF-α that avoids systemic toxicity.

True isolated perfusion of the lower limb cannot be performed from levels higher than the femoral vessels because of multiple pelvic collaterals, which anastomose with the limb circulation. Because of the risks associated with systemic TNF-α leakage, the authors perform isolated perfusion from the superficial femoral vessels and have not experienced the problems with systemic side-effects reported elsewhere[6]. Neither prophylactic dopamine infusion nor hyperhydration was required. The decision to use low-dose TNF-α was influenced by the previous report in which toxicity was associated with high dosage. The complete tumour response and absence of systemic side-effects in the present series endorse this decision. Similarly, although there is an experimental precedent for the use of IFN-γ with TNF-α, in practice the combination is unnecessary.

In the sole patient in whom systemic leakage of rTNF-α was documented[9], the systemic arterial concentration of the cytokine remained much lower than the mixed venous level. It follows that passage through the lungs results in clearance of TNF-α from the circulation, which may be of importance in the development of adult respiratory distress syndrome.

Patients with particularly bulky tumours were selected because of potential local tissue damage, as in these patients amputation would have been an acceptable treatment option. The three patients with the most extensive disease ultimately required above-knee amputation because of the large soft tissue defects, which failed to heal after tumour necrosis. Impaired skin healing has been a feature in this series. Three patients, including one who underwent amputation, developed superficial necrotic ulcers, which failed to heal after several months.

A side-effect common to the first seven patients in the present study was oedema of the perfused limb giving rise to symptoms of compartment syndrome. The dose of rTNF-α was decreased during the course of the series in the hope of reducing local morbidity, a manoeuvre that was successful. In the last two patients the effects of oedema were further reduced by prophylactic fasciotomy.

For isolated limb perfusion to be considered successful, whichever combination of drugs is used, there must be a high percentage of complete tumour response accompanied by minimal levels of systemic and local toxicity. This objective has been achieved in the present series, with particularly gratifying results in three of the four patients with soft tissue sarcoma who otherwise could only have been offered amputation. Careful selection of patients for isolated limb perfusion with rTNF-α and melphalan is important. The potential for tissue loss and inhibition of healing needs to be carefully weighed against the benefits of treatment with rTNF-α. The possibility of long-term ulceration should be taken into account, and caution must be exercised if a patient has lost skin cover owing to tumour infiltration or is at risk of doing so. Where the lesion is so extensive that its necrosis will result in a large tissue defect not amenable to plastic reconstruction, another treatment option should be sought.

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Management of malignant melanoma of the head and neck

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A total of 91 patients with melanoma of the head and neck treated between 1973 and 1991 were studied prospectively with regard to prognostic features, treatment and outcome. Other than Breslow thickness, the only important prognostic feature was the less aggressive nature of lentigo maligna melanoma. A policy of selective excision margins, 1 cm for impalpable and 2 cm for palpable lesions, was found to be safe, although preliminary biopsy should be used if there is diagnostic uncertainty or where the expected extent of surgery entails a mutilating procedure. Local recurrence rates were not affected by the method of wound closure, which should be determined by the best functional and cosmetic outcome. These results support the trend against prophylactic neck dissection. Such dissection, when indicated for lesions of the face, pinna, anterior scalp and parotid area, should routinely include superficial parotidectomy. Uncontrolled symptomatic loco-regional recurrence is an uncommon complication that may occur despite radical primary surgery. The role of preoperative radiotherapy for high-risk melanoma in this situation warrants investigation.

Malignant melanoma has been doubling in incidence every decade since the early 1960s[1–3]. Currently, adequate surgical excision of the primary tumour is the only effective treatment for most melanomas, and is curative for thin lesions[4,5]. Controversy exists as to what constitutes an adequate excision margin, the safety of flap reconstruction and the place of elective lymph node dissection. For melanoma of the head and neck these issues are particularly important because of the premium placed on cosmesis and the preservation of anatomical structures.

This paper reviews an 18-year experience with a policy of selective excision margins based on clinical estimation of tumour thickness as previously described[6]. Wound reconstruction was planned to achieve the optimum cosmetic and functional result, with no restriction placed on the use of local flaps.

Patients and methods

A total of 664 patients with melanoma were studied prospectively in a dedicated clinic between 1973 and 1991. Some 91 patients had lesions on the head or neck and were reviewed with regard to site, histological type, clinical and histological assessment of thickness, staging, treatment, pattern of recurrence and survival. Details of these 91 patients are given in *Table 1*. Six patients had nodal disease at presentation and three presented with distant metastases.

Preoperative assessment of tumour thickness was possible for 88 lesions; 34 were judged impalpable (thin) and 54 palpable (thick).

Treatment policy

The excision margin was based on preoperative clinical assessment of tumour thickness[6]. Nineteen patients underwent preliminary excisional biopsy, six incisional biopsy and five peroperative frozen-section biopsy. In 61 patients definitive treatment followed clinical diagnosis.

Initially, impalpable lesions were excised with a 1-cm margin, palpable but not overtly nodular tumours with a 2-cm margin and overtly nodular lesions with a 3–5-cm margin (group 1 in *Table 2*). From January 1987 the margin for nodular lesions has been reduced to 2 cm (group 2 in *Table 2*). The current policy is to excise impalpable tumours with a 1-cm clearance and palpable lesions with a 2-cm margin. It was occasionally necessary to sacrifice adherence to this margin policy to preserve important anatomical features, while trying to observe adequate clearance in the direction of the draining lymphatics. Lentigo maligna was excised with a 0·5-cm margin, with an optimum 2-cm clearance applied only to any palpable element within it. Handling of the tumour was avoided during surgery and the wound was irrigated with a cytotoxic solution of 1:5 buffered sodium hypochlorite before closure.

The method of wound reconstruction was chosen to produce the best functional and cosmetic result with no restriction placed on the use of local flaps (*Table 3*).

In selected patients with locally advanced disease with a poor prognosis, the use of a deltopectoral or, more recently, pectoralis major myocutaneous flap allowed radical resection and in-continuity nodal dissection as a palliative measure.

Eight therapeutic radical neck dissections were performed: two as a primary procedure and six for recurrent disease; three included superficial parotidectomy.

Table 1 *Details of 91 patients with melanoma of the head and neck*

Sex ratio (M:F)	44:47
Mean (range) age (years)	63·5 (22–89)
Site	
Face	73
Neck	16
Scalp	2
Histological type	
Superficial spreading melanoma	24
Nodular melanoma	28
Lentigo maligna melanoma	26
Lentigo maligna	13
Thickness	
In situ	20
≤0·75 mm	14
0·76–1·49 mm	10
1·5–3·9 mm	27
≥4·0 mm	20

Table 2 *Influence of change in excision margin policy on local recurrence rate*

	Group 1*	Group 2†
No. of patients	54	37
Mean Breslow thickness (mm)	2·00	1·94
Local recurrence	8 (15)	2 (5)

Values in parentheses are percentages. *Patients treated before 1987, upper policy margin 3–5 cm; †patients treated from 1987, upper policy margin 2 cm

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Table 3 *Methods of wound reconstruction*

	No. of patients
Direct suture	25
Local flap	40
Distant flap	3
Full-thickness skin graft	10
Split skin graft	9
Local flap plus split skin graft	1
Biopsy only (lentigo maligna)	3

Table 4 *Influence of Breslow thickness on recurrence rate*

Thickness (mm)	No. of patients	Patients with recurrence
≤0·75	14	0 (0)
0·76–1·49	10	2 (20)
1·5–3·9	27	12 (44)
≥4·0	20	10 (50)

Values in parentheses are percentages

Prophylactic neck dissection was carried out selectively for nodular melanoma in fit patients and when an in-continuity resection could be achieved. Eleven prophylactic dissections were performed, three of which included superficial parotidectomy.

Results

Preoperative clinical assessment

The clinical estimate of tumour thickness correlated well with histological measurement. Of the 34 lesions considered impalpable (and therefore suitable for a 1-cm excision), 31 were ≤0·75 mm thick on histological assessment and three <1 mm thick. Of the 47 palpable lesions, four were ≤0·75 mm thick but these were all either lentigo maligna or lentigo maligna melanoma and in all cases the diagnosis was clinically obvious. No patient, therefore, had an inappropriately wide excision as a result of clinical overestimation of tumour thickness.

Survival and prognostic features

The overall cumulative survival rate for those with invasive melanoma was 70·2 per cent at 5 years and 47·2 per cent at 10 years. As with other studies[4,5,7–10], Breslow thickness was the most important determinant of prognosis (*Table 4*).

When matched for thickness, the site of the primary tumour was not a significant prognostic factor.

Statistical analysis was not possible owing to the small numbers but lentigo maligna melanoma appeared to be a less aggressive tumour compared with nodular or superficial spreading melanoma. Only three of 26 patients with lentigo maligna melanoma died from melanoma and the only two long-term survivors after systemic recurrence were in this group (see below).

Local recurrence

Ten patients had local recurrence; these all had thick (2·2–9·9 mm) tumours of poor prognosis. In two cases, re-excision was followed by prolonged survival; in the remaining eight patients, systemic or nodal recurrence either preceded local recurrence or supervened within 2 months, suggesting that more radical primary surgery would have made little difference. Four of these patients died with uncontrolled symptomatic locoregional disease.

Reduction of the maximum excision margin to 2 cm since 1987 did not lead to an increase in the rate of local recurrence (*Table 2*). For excision defects that could not be closed directly, the method of reconstruction did not significantly affect the local recurrence rate (six of 31 patients with a flap compared with three of 19 with a skin graft).

Regional recurrence

Regional recurrence was seen in 13 patients. All cases occurred with primary tumours ≥2 mm in thickness and five were associated with primaries in the parotid region of the face or neck.

Patients with regional recurrence fared better than those with local recurrence; in particular, all five patients who had regional recurrence in the absence of local recurrence remain alive at 41–160 months.

Eleven patients underwent prophylactic neck dissection as part of the initial treatment, of whom two subsequently developed regional recurrence. Both had primaries in the parotid region of the face or neck and developed parotid recurrence after radical neck dissection that included either a lower pole excision only or no parotidectomy. Only two of the 11 prophylactic neck dissections revealed occult metastases.

Adjuvant therapy

Three patients received adjuvant local radiotherapy as part of the initial treatment. In two patients, both with thick (4·2 and 4·5 mm) rapidly growing melanomas, preliminary radiotherapy was given in the hope of preventing early local recurrence after subsequent resection. One of these patients is alive without recurrence at 48 months and the second died at 51 months, disease-free. A third patient with an extensive ulcerated lentigo maligna melanoma of the scalp received radiotherapy as primary treatment because his general condition precluded major surgery.

Discussion

The minimum adequate excision margin for melanoma is unknown, but extremely wide clearance is unnecessary[6,11–13]. One-stage definitive excision based on clinical estimation of tumour thickness[6] can be safely applied to tumours of the head and neck. Impalpable (≤0·75 mm thick) lesions should be excised with a 1-cm margin. For palpable tumours (≥0·76 mm thick), a 2-cm margin results in no increase in local or distant recurrence rate compared with wider excisions; this can safely be reduced to 1 cm in one direction to spare important anatomical features while taking a wider margin in the direction of draining lymphatics. Where there is uncertainty, or potentially mutilating surgery is envisaged, preliminary biopsy should be carried out to confirm the diagnosis. One-third of the present patients underwent preliminary biopsy and none had an excessive clearance because of clinical overestimation of depth. The only patient who, inadvertently, had an invasive melanoma treated by an excision margin <1 cm had local recurrence. Where local recurrence occurred, it was generally preceded by (or was simultaneous with) regional or systemic disease, suggesting that recurrence was more a marker of aggressive disease than the result of inadequate surgery.

Provided the lesion is adequately excised, the method of reconstruction does not influence the local recurrence rate[14]. Small defects can be closed directly. For larger defects local flaps provide a better colour and texture match. Inappropriate use of split skin grafts causes cosmetic distress to patients after melanoma excision[15].

Uncontrolled locoregional disease is distressing and radical palliative resection may be indicated even when the prognosis is poor. Myocutaneous flaps may provide reliable primary healing and a minimum inpatient stay. A recent retrospective review of routine preoperative radiotherapy in patients with primary melanoma[16] did not show any advantage in terms of survival or local control but this has not been assessed in the prevention of uncontrolled locoregional recurrence in rapidly growing nodular melanoma. In three of the present patients local control was achieved by a combination of radiotherapy and surgery; further study of this approach is warranted.

The arguments for and against elective lymph node dissection have been summarized[17] but were not specifically addressed by the present study. Prophylactic neck dissection was carried out only for nodular melanoma in patients who were fit and in whom an in-continuity resection could be performed. Of 11 patients who underwent prophylactic dissection, two demonstrated occult disease and a further two developed regional recurrence in the parotid nodes. The latter occurred early in the series and superficial parotidectomy is now carried out for melanoma of the face, pinna, anterior scalp and parotid region of the neck[18–21]. The low incidence of nodal involvement allows avoidance of routine prophylactic dissection for any group of melanoma.

Despite advances in immunotherapy and chemotherapy, adequate surgery provides the only effective treatment of primary melanoma. A policy of selective excision margins and cosmetic wound closure is oncologically sound and minimizes unnecessary mutilation.

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Specimen-orientated radiography helps define excision margins of malignant lesions detected by breast screening

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Eighty patients with impalpable breast lesions detected by mammographic screening underwent hookwire-guided wide local excision. Excision specimens were orientated with Ligaclips and submitted to radiography; if, on the specimen radiograph, the mammographic lesion crossed any visible margin, further tissue was excised. Clear histological margins were obtained on the initial excision in 52 (68 per cent) of 77 carcinomas. After inspection of the orientated specimen radiograph, further tissue was excised from 22 patients; this significantly increased the rate of complete excision to 86 per cent (P < 0·01). Significantly more patients with invasive cancer had a complete excision than those with ductal carcinoma in situ *(52 of 57* versus *14 of 20, P < 0·02).*

he excision of impalpable lesions detected by mammography an be inadequate in up to 60 per cent of patients with invasive r *in situ* cancer[1,2]. Stereotactic and ultrasonographically uided fine-needle aspiration cytology helps to identify nalignant lesions before surgery[3]. The majority of these lesions nvolve small areas of the breast and should be suitable for reatment by wide local excision. The recently described nethod[4] of orientating specimen radiographs with Ligaclips Ethicon, Edinburgh, UK) suggested that this technique may elp determine whether the mammographic lesion has been ompletely excised. This method allows further tissue to be emoved to achieve a complete excision at the first operation.

This study examined whether this technique results in an mprovement in the complete excision rate of impalpable creen-detected breast cancer.

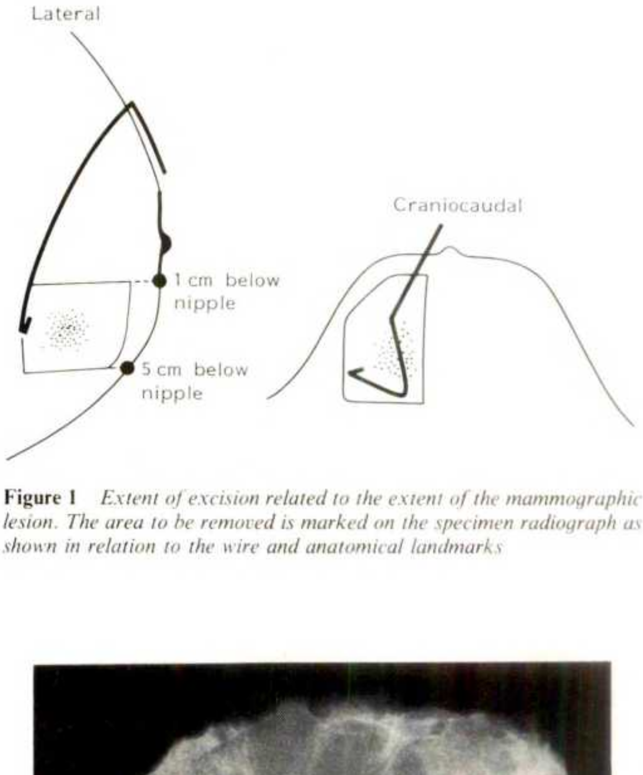

Figure 1 *Extent of excision related to the extent of the mammographic lesion. The area to be removed is marked on the specimen radiograph as shown in relation to the wire and anatomical landmarks*

atients and methods

ighty patients of median age 58 (range 50–64) years underwent tereotactic (75 patients) or ultrasonographically (five) guided ookwire localization wide local excision over a 2-year period. Wide cal excision was performed because of malignant (49 patients) or uspicious (23) stereotactic or ultrasonographically guided fine-needle spiration cytology or because malignant mammographic characteristics ere found in the presence of acellular (seven) or benign (one) cytology. he main mammographic lesion was a mass in 25 patients, a arenchymal distortion in 12, microcalcification in 32 and microcalcifiation associated with a mass lesion or parenchymal distortion in 11. issue was excised anterior to the lesion to the level of the subcutaneous t and posteriorly to the pectoral fascia using the method illustrated *Figure 1*. After removal, the specimen was orientated with Ligaclips one placed on the anterior, two on the medial and three on the inferior argin) and radiographed on an IGE-Senex mammogram machine GE/SGR, Staines, France), orientating the specimen so that the osterior surface was in contact with the table-top (*Figure 2*). adiography was performed after compression to a pressure of 2 mbar. n inspection of the specimen radiograph, if the visible lesion crossed ny margin, further tissue was excised from the appropriate area, rientated and radiographed.

The external surfaces of the specimen were inked and the specimen laced on a trimming jig with the anterior surface uppermost. Serial lices 4 mm thick were taken in a plane parallel to the chest wall and e slices radiographed. Appropriate areas were blocked to include ll six possible resection margins and all areas of radiological bnormality[5]. Excision was considered complete if there was no invasive r *in situ* disease within 1 mm of any resection margin on histological ssessment and the radiologist was satisfied that all mammographic bnormalities were contained in the specimen radiograph[6].

Statistical analysis was performed using the χ^2 test.

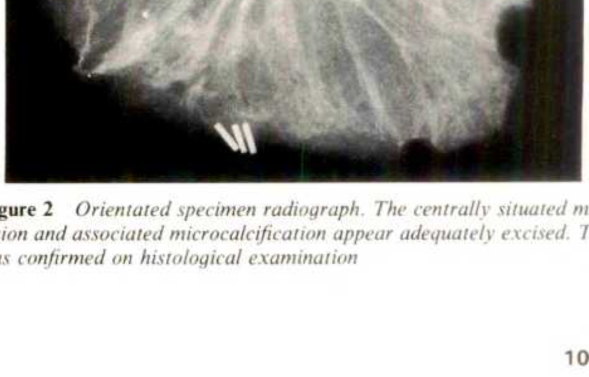

Figure 2 *Orientated specimen radiograph. The centrally situated mass lesion and associated microcalcification appear adequately excised. This was confirmed on histological examination*

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Table 1 *Findings on re-excision after inspection of orientated specimen radiograph and influence of further excision on overall complete excision rate*

	No.
Patients with invasive or *in situ* carcinoma	77 (100)
Clear margins on first excision	52 (68)
After inspection of specimen radiograph	
Further tissue excised	22
Further invasive carcinoma on re-excision	1
Further *in situ* carcinoma on re-excision	3
Initial excision close; no residual disease	10
No disease in further specimen; initial margins clear	8
Clear margins after second excision	66 (86)

Values in parentheses are percentages

Results

Rates of complete excision

The mammographic lesion was present in the first excision specimen in 79 patients and in the second in one. Subsequent histological examination showed that 77 of the 80 lesions were malignant: 20 were *in situ* carcinoma, all of ductal type, and 57 invasive carcinoma. Clear histological margins were obtained on the excision specimen containing the mammographic lesion in 52 (68 per cent) of the 77 carcinomas. Further tissue was excised in 22 patients as a result of inspecting the specimen radiograph; 15 patients had one extra piece of tissue removed and seven two further areas of excision. A small focus of invasive carcinoma was present in the re-excision specimen in one patient and three had *in situ* disease in the additional tissue removed. In none of these patients did this disease reach the new excision margins. In ten of the 22 patients *in situ* or invasive disease was identified within 1 mm of the initial margin of excision, but no residual carcinoma was identified in the further excision (*Table 1*). As a result of these further excisions 66 patients (86 per cent) had a complete excision, a significant increase ($P < 0{\cdot}01$) compared with the initial rate of complete excision.

Factors affecting complete excision

Significantly more patients with invasive cancer had a complete excision than those with ductal carcinoma *in situ* (52 of 57 *versus* 14 of 20, $P < 0{\cdot}02$).

There was no statistical association between the mammographic lesion and the rate of complete excision (mass, 92 per cent; distortion, 89 per cent; microcalcification, 78 per cent; microcalcification plus mass lesion or parenchymal distortion, 90 per cent).

Discussion

Mammography is a reliable method of detecting impalpable non-invasive breast carcinoma[7]. In patients with localized areas of non-invasive disease, complete excision may be all that is required[8,9]. The accurate orientation of wide local excision specimens in patients with palpable breast abnormalities has been emphasized[10]. The present study demonstrates that, by accurate orientation of impalpable specimens, the proportion of completely excised carcinoma can be significantly increased.

Others[2,11] have emphasized the importance of specimen radiology to ensure that a mammographic lesion has been excised. In palpable lesions, specimen radiography differentiates between involved and non-involved areas of breast tissue[12] but a recent study using two-dimensional radiography showed that this technique is poor in detecting the extension of malignancy to resection margins[13]. A major problem was experienced in the technique used to obtain two-dimensional radiographs in maintaining the specimen in a fixed position; this reduced the quality of the specimen radiograph to such an extent that in many instances the lesion could not be visualized[13]. Using a machine with a moving grid and applying compression to the specimen it has proved possible to obtain high-quality radiographs that provide clear visualization of the mammographic lesion and allow assessment of margin involvement.

It has previously been suggested that needle localization biopsy should not be considered as a therapeutic procedure and should be used solely for diagnosis[2]. The present study shows that wide local excision of impalpable lesions is associated with a similar rate of complete excision to that of palpable lesions. Mammography frequently underestimates the extent of involvement with *in situ* disease that extends beyond the limit of the mammographic lesion[14], and this phenomenon was seen in the present study.

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Scar formation after breast-conserving surgery for cancer

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A study of surgery for breast cancer was performed to examine the influence of haematoma formation and radiotherapy on the development of mammographically detected scars. Fifty-nine women undergoing lumpectomy and radiotherapy were studied. Sixteen had mammographic scars 12 months after surgery. There was a correlation between postoperative haematoma formation and scarring (P = *0·03*) *but not between tumour size and scarring. The type of radiation therapy did not influence scar formation.*

ne of the most difficult problems in the management of atients after lumpectomy and radiotherapy is the early etection of recurrence or residual disease. It can be difficult o distinguish postoperative scarring from recurrent or residual umour by mammography. The aim of this study was to assess he prevalence of scar formation after lumpectomy and adiotherapy, and to determine whether haematoma formation nfluences scar development.

atients and methods

retrospective study of 59 women who underwent lumpectomy and adiotherapy for breast cancer between June 1984 and February 1989 as carried out. The study included those for whom preoperative and llow-up mammograms could be obtained for review and on whom adiotherapy-planning computed tomography (CT) had been performed.

Surgical treatment consisted of local excision with axillary node learance. In all, 56 women underwent lumpectomy and three uadrantectomy. The mean age at the time of surgery was 46 (range 5–72) years.

The tumour size was <2 cm in 46 patients, 2–5 cm in 11, >5 cm n one and unrecorded in one.

Postoperative radiotherapy was administered at a dose of 45 Gy, elivered in 25 fractions over 5 weeks, followed by a booster dose of 0 Gy in ten fractions over 2 weeks in 45 patients, or iridium wire nplantation in 14. Adjuvant chemotherapy was given to 17 patients.

Planning of treatment used CT of the breast, axilla, supraclavicular egion and underlying lung, performed a mean of 24 (range 9–77) days fter operation.

Follow-up included physical examination and mammography craniocaudal, mediolateral and oblique views) performed at 6- and 2-month intervals. The mean follow-up was 28 (range 6–72) months.

The planning CT scans and mammograms were reviewed ndependently by two radiologists. The mammograms were separated om the tomograms and studied without knowledge of the radiological orrelation or clinical outcome of the individual patient.

Breast haematomas detected on CT were defined as rounded w-density areas with ill defined margins and subtle changes in the urrounding breast tissue (*Figure 1*). Haematomas were measured in entimetres and those <1 cm in diameter excluded. Lymphoceles were oted in the axilla in 50 per cent of patients as areas of lower density ith discrete margins.

Mammograms were scored on the following scale: 0, normal; 1, istortion, but no increase in density or mass; 2, mild localized increase n density; 3, moderate localized increase in density; and 4, gross ocalized increase in density. Mammographic scarring was considered o be present when a localized increase in density was present (score , 3 or 4) (*Figure 2*).

esults

f the 59 patients reviewed, 16 had a visible scar on ammography 12 months after operation. Seventeen had a aematoma detected on planning CT. A haematoma or ammographic scar was not seen in 33 patients and both aematoma and scar were observed in eight. There was a significant association between the presence of postoperative haematoma and subsequent mammographic scarring ($\chi^2 = 4·57$, 1 d.f., $P = 0·03$).

Eleven of the reviewed patients had a tumour of size ≥2 cm and this was significantly associated with the presence of haematoma on CT ($\chi^2 = 4·17$, 1 d.f., $P = 0·04$). A correlation between the size of the tumour and the presence of mammographic scarring was not demonstrated ($\chi^2 = 0·59$, 1 d.f., $P = 0·45$).

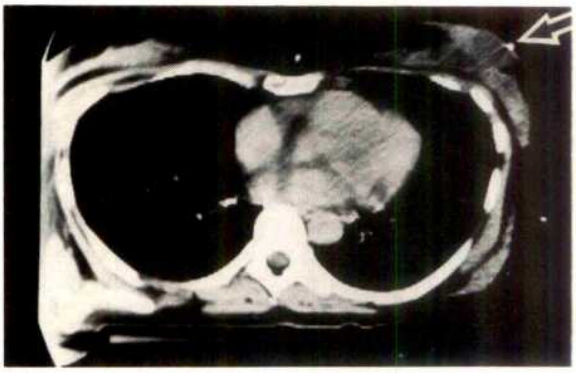

Figure 1 *Planning computed tomogram demonstrating a postoperative 2-cm haematoma in the left breast (arrow)*

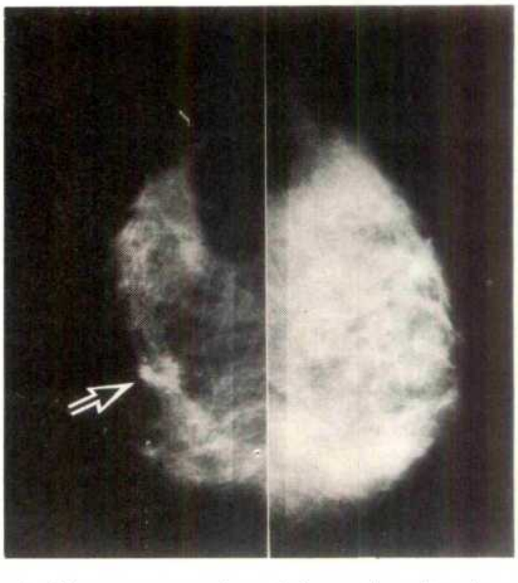

Figure 2 *Mammogram performed 6 months after lumpectomy, demonstrating a scar in the left breast (arrow) that was scored 4 and confirmed to be fibrosis by fine-needle biopsy*

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A total of 44 pathology reports were available for review. Eight of 31 patients with adequately cleared margins and seven of 13 with *in situ* or invasive carcinoma 'close to' a margin subsequently developed mammographic scar formation ($\chi^2 = 3{\cdot}12$, 1 d.f., $P = 0{\cdot}08$). The measured diameter of the excised specimens had no significant association with haematoma detected on CT (six of 19 specimens $\leqslant 5$ cm in diameter, eight of 25 >5 cm; $\chi^2 = 0{\cdot}001$, 1 d.f., $P = 0{\cdot}98$). Similarly, no significant association between specimen diameter and subsequent mammographic scar formation was demonstrated (eight of 19 specimens $\leqslant 5$ cm in diameter and eight of 25 >5 cm; $\chi^2 = 0{\cdot}80$, 1 d.f., $P = 0{\cdot}37$).

The method of boost delivery with either electron beam (45 patients) or iridium wire (14) had no significant association with the incidence of subsequent mammographic scar formation ($\chi^2 = 0{\cdot}52$, 1 d.f., $P = 0{\cdot}47$).

Two patients underwent further surgery to the same breast for suspicious abnormalities on follow-up mammography. Local residual disease was detected in one of these patients, in whom the mammograms at 6 and 12 months after operation were scored as mild localized increase in density. No haematoma was seen on planning CT. The other patient had a 4-cm haematoma on CT and gross localized increase in density at the excision site, persisting on follow-up mammography at 18 months. Histological examination of the excision biopsy demonstrated radiation fibrosis.

Discussion

Mammography is important in the follow-up of women in whom breast cancer has been treated by lumpectomy and radiotherapy[1-3]. The mammographic changes following surgery and radiotherapy include skin thickening, increased parenchymal markings and a stellate or mass-like density at the surgical site[1,4,5]. These architectural distortions may be associated with skin retraction and areas of calcification, but it is often difficult to differentiate these changes from recurrent or residual carcinoma[4]. The course of changes after surgery and irradiation[6] is to regress or stabilize over time, with maximal change at 1 year and gradual regression over 2–3 years.

Local recurrence of breast cancer occurs at a rate of 1–2 per cent per year, and the majority of tumours (67 per cent) will occur at or near the excision site[2,7]. The fact that 25 per cent of recurrences are detected by mammography alone[2], and are more likely to be less invasive than those detectable on physical examination, emphasizes the importance of early detection. Haffty *et al.*[2] reported a high rate of long-term survival in those with recurrence or residual disease treated by mastectomy or repeat local resection.

Postoperative haematoma detectable on radiotherapy planning CT has previously been reported[8]. Sadowsky *et al.* commented that aspiration of large haematomas reduced the amount of long-term postoperative distortion, making it easie to examine the tumour bed after irradiation. Figures were not given to justify this statement. Although most haematomas resolve within 2–4 weeks after surgery, they may continue a small ill defined densities that cannot be differentiated from residual or recurrent tumour[1]. The association between increased tumour size and the presence of postoperative haematoma could be explained by the greater area of surgical resection and remaining dead space. A significant association between the presence of postoperative haematoma and sca formation on follow-up mammography at 12 months wa demonstrated in the present study. Boost delivery with electron beam or iridium wire implantation had no influence on subsequent scar formation.

Haematoma is associated with increased mammographic scar formation. The type of radiation and size of tumour are not significant factors.

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Effects of surgery on the generation of lymphokine-activated killer cells in patients with breast cancer

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Natural killer (NK) cell activity and the capacity to generate lymphokine-activated killer (LAK) cell activity were studied in 43 patients with operable breast cancer before and after surgery. Results were compared with those from ten healthy subjects. Patients with breast cancer had normal LAK and NK cell activity before surgery. A subgroup of patients with stage III disease had depressed LAK cell activity ($P < 0{\cdot}013$). NK cell activity decreased by over 50 per cent on the first day after surgery and did not return to preoperative levels by day 7 ($P < 0{\cdot}0005$). Generation of LAK cell activity was unaffected by surgery. The addition of 10 per cent autologous plasma to the culture medium during the induction of LAK cell activity in vitro *did not suppress LAK cell activity in patients with breast cancer. These results suggest that perioperative adjuvant immunotherapy based on interleukin 2 and LAK cells is not ruled out by systemic suppressive effects from either cancer or surgery.*

Immunotherapeutic treatment of malignancy using interleukin (IL) 2 has been studied in some detail since the first clinical trial was reported by Rosenberg *et al.*[1]. Initial enthusiasm was stimulated by the encouraging results of treatment with IL-2 and lymphokine-activated killer (LAK) cells in patients with metastatic renal cancer and melanoma[1–3]. Subsequent reports of the severe potential toxicity of the regimen, the cost and logistical difficulty of providing the treatment, and the low and unpredictable response rate[4–7] diminished this enthusiasm.

A review of the evidence from animal models may be useful in suggesting possible causes for the disappointing results. The toxicity of IL-2 is less in mice and equivalent doses cannot be used clinically[8]. Human subjects frequently have advanced disease whereas animal models have used tumour at an early or occult stage. Many human studies have not used LAK cells with IL-2, despite experimental evidence for synergism between the lymphokine and LAK cells in a tumoricidal capacity[9,10]. There are considerable logistical problems involved in the use of LAK cells but the only substantial comparison of treatment with and without such cells[11] suggests that complete remission is more frequent with LAK cell treatment.

The unique antitumour cytotoxic activity of LAK cells was the basis for early studies of IL-2-based immunotherapy[8]. It is now clear that this direct cytolytic activity is unlikely to play a major role in the tumour regression observed clinically and experimentally. LAK cells do not migrate to tumour tissue[12] and are found there relatively infrequently even in recently treated responding lesions[13]. The exact role of these cells is therefore unclear. LAK cells are active secretors of cytokines, particularly γ interferon and tumour necrosis factor α[14], and may bring about tumour cell destruction indirectly, by affecting the activity of other parts of the immune system. It has been shown, for example, that LAK cells modulate a T cell-mediated immune response in the mouse[15].

Suppression of the generation of LAK cell activity by immunosuppressive substances produced by the tumour has been thought to be a cause of treatment failure, and there is a reduced capacity to generate LAK cells in patients with advanced cancer[16,17]. *In vitro* studies have shown that several tumour cell lines secrete substances capable of inhibiting LAK cell generation[18,19]. The clinical findings may result partly from cancer-associated malnutrition, and the relevance of the LAK cell-inhibiting substances *in vivo* remains uncertain. These findings suggest that LAK cell–IL-2 treatment might be most effective in an adjuvant setting, after surgical debulking of a tumour. Surgery has transient suppressive effects on several components of the immune system, including T cell numbers and natural killer (NK) cell function[20–23], and an adverse effect on LAK cell production in response to IL-2 in some groups of patients[24]. Before considering adjuvant perioperative LAK cell–IL-2 treatments, possible suppressive effects on LAK cell generation of factors from the tumour, and of surgery itself, must be defined. This study defines these effects in a relatively homogeneous group of patients with breast cancer.

Patients and methods

Patients

Patients with operable breast cancer of Union Internacional Contra la Cancrum (UICC) stages I–III were studied in the perioperative period. Control subjects comprised healthy laboratory workers. None of the subjects studied was suffering from clinically evident acute bacterial or viral infection at the time of sampling, and none was taking corticosteroids, azathioprine or cyclosporin.

Samples

Samples (20 ml) of venous blood were collected into lithium heparin tubes and allowed to cool to room temperature. Mononuclear cells obtained by density centrifugation over Histopaque 1077 (Sigma Chemicals, Poole, UK) were washed twice in RPMI 1640 (Gibco, Paisley, UK) medium, resuspended in the same medium with 10 per cent heat-inactivated fetal calf serum (FCS) (Gibco), and numbers and viability assessed. Samples were taken on the morning of surgery, and on the first, seventh and 28th mornings after surgery.

Lymphokine-activated killer cell generation

Peripheral blood mononuclear cells (PBMCs) were resuspended at a density of 10^6 cells ml^{-1} in RPMI 1640 medium containing 10 per cent FCS, 200 units ml^{-1} recombinant human IL-2 (Glaxo, Geneva, Switzerland) and antibiotics (penicillin 50 $\mu\text{g ml}^{-1}$, streptomycin 50 $\mu\text{g ml}^{-1}$ and amphotericin 0·125 $\mu\text{g ml}^{-1}$). Cells were cultured for 72 h at 37°C in an atmosphere containing 5 per cent carbon dioxide. Cultured cells were harvested, washed twice in RPMI, and numbers

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and viability reassessed. They were then used as effector cells in cytotoxicity assays.

Cytotoxicity assays

LAK cell activity was measured in a standard 4-h chromium-release assay[16]. DAUDI target cells labelled with 2 MBq ^{51}Cr per 10^6 cells were exposed to effector cells at three different effector:target ratios, usually 6·25:1, 12·5:1 and 25:1. Results at all ratios tested were concordant.

The mean(s.d.) spontaneous:maximal ^{51}Cr release ratio in the LAK cell assays performed was 15·4(5·5) per cent.

Addition of autologous plasma

Autologous plasma was stored from each blood sample taken. Cytotoxicity assays using effector cells that had been cultured in the presence of 10 per cent autologous plasma were compared with assays using untreated IL-2-stimulated effectors.

Natural killer cell assay

NK cell activity of PBMC preparations was measured immediately after initial separation and washing of the cells. A 4-h chromium-release cytotoxicity assay was used as described above, using the K562 cell line as target.

Nutritional indices

Height and weight were recorded in patients and the body mass index derived. Upper-arm skinfold thickness and serum albumin levels were determined. Malnutrition was defined as a value below the fifth centile of two or more of these three parameters.

Statistical analysis

Comparison between patients with cancer and controls was carried out by the Mann–Whitney *U* test, and of results from the former group at different times by the Wilcoxon signed rank test. LAK cell cytotoxicity in stage subgroups was compared using Student's *t* test.

Results

Patient population

The study population comprised 43 patients with breast cancer and ten normal healthy volunteers. The mean ages of the two groups were 61 and 27 years respectively. Eighteen breast cancers were UICC stage I, 20 stage II and five stage III. Only two patients with cancer were malnourished.

Effects of cancer on lymphokine-activated killer cell generation

The median cytotoxicity at an effector:target ratio of 12·5:1 was 67 per cent for the patient group compared with 64 per cent for the normal volunteers. This difference was not significant ($P < 0·42$, Mann–Whitney *U* test). *Table 1* shows these effects for patients with different stages of disease. Separate analysis of the effects of plasma from patients with stage III tumours on the cytotoxicity assay did not reveal any suppressive activity (median cytotoxicity 54 per cent without plasma, 61 per cent with 10 per cent autologous plasma). NK cell activity was not suppressed before operation in this subgroup.

Table 1 *Effects of cancer on lymphokine-activated killer cell generation*

	No.	Median (range) cytotoxicity at an effector:target ratio of 12·5:1 (%)
Control subjects	10	64 (27–84)*
Patients with breast cancer		
Stage I	18	64 (24–83)†
Stage II	20	70 (36–79)‡
Stage III	5	48 (32–71)
Total	43	67 (24–90)

*$P < 0·42$ (control *versus* breast cancer group, Mann–Whitney *U* test); †$P < 0·05$ (stage I *versus* stage III, $t = 2·09$, 21 d.f.); ‡$P < 0·013$ (stage II *versus* stage III, $t = 2·55$, 23 d.f.)

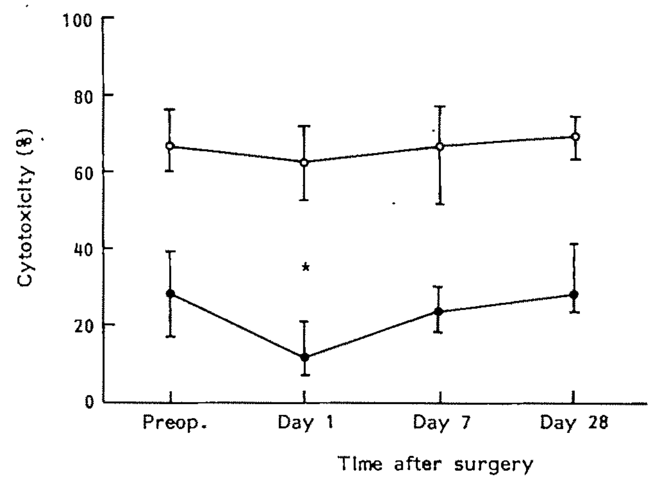

Figure 1 *Effect of surgery on* in vitro *cytotoxicity of lymphokine-activated killer* (○) *and natural killer* (●) *cells. Results of a 4-h ^{51}Cr-release assay at an effector:target ratio of 12·5:1.* *$P < 0·0005$ (*Wilcoxon rank sum test*)

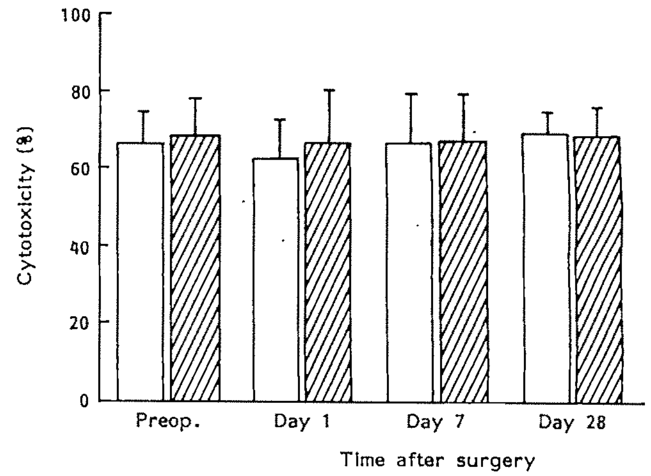

Figure 2 *Effect of autologous plasma on generation of lymphokine-activated killer cell cytotoxicity. Results of a 4-h ^{51}Cr-release assay at an effector:target ratio of 12·5:1. Values are median (semi-interquartile range).* □, *No plasma;* ■, *10 per cent autologous plasma*

Effects of surgery on lymphokine-activated killer cell generation

LAK cell cytotoxicity against DAUDI target cells was not altered by surgery in these patients, but NK cell activity was suppressed (*Figure 1*). Sixteen patients underwent wide local excision of the tumour and 27 simple mastectomy; all patients had axillary clearance to level II. There was no significant difference in LAK or NK cell activity between these two subgroups at any of the intervals studied.

Effects of autologous plasma

The addition of 10 per cent autologous heparinized plasma during the 3-day incubation period *in vitro* did not affect LAK cell cytotoxicity at any time (*Figure 2*).

Discussion

Previous studies[16,17] have described a decrease in the ability of patients with gastric or colonic cancer to generate LAK cell responses when stimulated with IL-2. The present study, however, found no deficiency in the potential for LAK cell activity generation before surgery. In the small number of patients with locally advanced disease there did appear to be some reduction in cytotoxic capacity; this result is similar to the findings of other workers, whose patients had disease of comparable average severity. Nutritional status influences lymphocyte function[25], which may explain the differences found between the present and previous studies. Only two of the present patients were clinically malnourished (one with stage I and one with stage III disease), compared with one-third of patients undergoing surgery for gastrointestinal malignancy[16].

Tumour cell lines cultured *in vitro* can produce soluble factors that cause profound inhibition of LAK cell activity[19,26]. In the present study there was no detectable inhibitory effect from the plasma of patients on the generation of LAK cells. The mechanisms by which LAK cell therapy causes tumour regression *in vivo* are not well defined, and it is possible that the efficacy of LAK cell treatment is inhibited by tumour-derived suppressor molecules acting locally.

Surgery has a suppressive effect on the immune system[19–23] but the changes vary widely in nature, duration and severity, and may be secondary to the neuroendocrine response to physiological stress. Surgery for gastrointestinal cancer suppresses LAK cell generation responses to IL-2 for several days, and such patients already have subnormal responses to IL-2 before surgery[24,27]. NK cell function was depressed after surgery for up to 7 days in the present study, confirming the findings of others[22,24]. This indicates that the surgery performed on these patients was sufficiently major to initiate some of the expected suppressive responses, an important point in view of the subjectively lesser severity of breast *versus* gastrointestinal cancer surgery. LAK cell generation in the patients in the present study was not affected by surgery (mastectomy or lumpectomy). This indicates that the number of functionally normal circulating precursor cells is not reduced, nor is their ability to respond to *in vitro* stimulation with IL-2. It should, therefore, be possible to generate LAK cells from patients' lymphocytes in the perioperative period. This would be important if adjuvant immunotherapy were a useful adjunct to surgery[28]. The information provided from these results is valuable, as it indicates that perioperative LAK cell–IL-2 treatment would not be rendered ineffective either by tumour-related factors or by the immunological effects of surgery.

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Short note

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Tuberculosis in the parotid region

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Tuberculosis of the parotid gland is rare, particularly when presenting as the sole focus of the disease. This paper presents five recent patients, none of whom had pulmonary infection and all of whom presented with 'lumps in the parotid'; one also had a facial nerve palsy.

Case reports

Patient 1

A 35-year-old student from Ecuador presented with a 4-month history of an enlarging swelling in the parotid region, associated with occasional pain. There was no history of tuberculosis and chest radiography was normal. Superficial parotidectomy was performed without complication. Histological analysis revealed the mass to be tuberculous involvement of an intraparotid lymph node.

Patient 2

A 51-year-old Irishman presented with an inflammatory swelling in the left neck with impending ulceration of the overlying skin, together with firmness of the left parotid gland and an incomplete facial palsy. Biopsy of the neck mass suggested a diagnosis of tuberculosis, and at operation a track was demonstrated running in the direction of the parotid gland. The Heaf test was strongly positive (grade 4) and chest radiography normal. Following antituberculous treatment the neck swelling and facial palsy resolved.

Patient 3

A 61-year-old Sikh woman presented with a mass and discharging sinus in the region of the right parotid gland. There was no lymphadenopathy and chest radiography was normal. Standard superficial parotidectomy was performed, which also included the sinus and surrounding skin, with primary wound healing. The diagnosis of tuberculosis was confirmed.

Patient 4

A 28-year-old Asian man presented with a 3-year history of a discrete swelling in the left parotid gland. Chest radiography was normal. Pleomorphic adenoma of the parotid gland was diagnosed but, while mobilizing the superficial lobe of the parotid, an enlarged high jugular lymph node was found. Frozen-section histological examination confirmed tuberculosis and the parotidectomy was abandoned.

Patient 5

A 54-year-old Turkish man presented with a sudden severe reduction in vision in the right eye and a 15-year history of a left parotid swelling that had recently enlarged and was now associated with a separate lymph node in the ipsilateral neck. His medical history included treatment for tuberculosis many years before, but the patient had ceased taking the medication after a couple of weeks because of associated indigestion. He was initially seen by an eye surgeon who found an ischaemic retinitis with neovasculature and was then referred to the authors' unit for assessment of the parotid mass. Tru-Cut (Travenol Laboratories, Thetford, UK) biopsy of the swelling confirmed the diagnosis of tuberculosis. The findings in the right eye are also consistent with a diagnosis of tuberculosis.

Discussion

Primary tuberculosis of the parotid gland is rare. Recent, mostly solitary, reports have come from the Middle East, Far East and Africa and also from Asian communities in Britain[1,2] and Canada[3]. The diagnosis is often difficult to make on clinical grounds[1,2] and emerges from histological analysis after superficial parotidectomy for presumed pleomorphic adenoma.

This series of five patients demonstrates the spectrum of possible clinical presentations. Patients may present with a discrete mobile mass in the parotid gland indistinguishable from a benign parotid tumour; the diagnosis is then made only after superficial parotidectomy[1,2]. Patient 3 presented with a swelling in the superficial lobe of the parotid gland in association with a discharging sinus to the overlying skin. Although the diagnosis of tuberculosis was suspected it was expedient to advise superficial parotidectomy; this confirmed the diagnosis and provided primary wound healing. Patient 2 presented with an incomplete facial nerve palsy, which has not been previously described. Only one of the patients in this series (no. 5) presented with or demonstrated pathology outside the parotid region. No patient had evidence of active pulmonary disease on chest radiography. Thus the possibility of tuberculosis must be considered in the differential diagnosis of parotid swelling, particularly in susceptible ethnic groups.

If tuberculosis is suspected, a biopsy such as Tru-Cut can help avoid an unnecessary operation[2]. Patients with a mass not entirely characteristic of a benign parotid tumour should undergo biopsy, either by Tru-Cut needling of the lesion or, if there is an associated lymph node, by lymph node excision[4]. It has been advocated that superficial parotidectomy be performed to remove the tuberculous material, as it is difficult to sterilize otherwise[3]. In the two superficial parotidectomies performed in the present series no technical difficulty was encountered and the wounds healed primarily. In the other three patients there was resolution of the disease on medical treatment without operation.

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Surgical reintervention for differentiated thyroid cancer

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Reoperation was performed in 110 of 185 patients with a differentiated thyroid carcinoma. In 25 patients (23 per cent) the indication for reintervention was a large thyroid remnant and in the other 85 (77 per cent) persistent or recurrent cancer was suspected. In 32 (29 per cent) of the 110 patients undergoing reoperation no evidence of cancer tissue was found. Tumour tissue in 33 patients (30 per cent) was resectable. Of 45 patients (41 per cent) with residual tumour after operation 24 showed only occult thyroid carcinoma with a raised serum thyroglobulin level. Eight of 21 patients with macroscopically persistent tumour died from the disease during a mean follow-up of 2·3 years. In 13 of 38 patients the investigated recurrent tumours were histologically less differentiated than the primary lesions, stressing the importance of total tumour clearance. The treatment of choice for persistent and recurrent differentiated thyroid carcinoma is surgical reintervention, if feasible, before radioiodine and radiation therapy are considered.

The treatment of persistent or recurrent differentiated thyroid carcinoma (DTC), whether follicular or papillary, consists of surgical reintervention, radioiodine therapy and external radiation[1–5]. All three methods can be used alternatively or in combination, but the timing and place of surgical reintervention need to be assessed[2,6–9].

The indications for reintervention are unanimously accepted for persistent and recurrent locoregional medullary thyroid carcinoma[10]. This is not the case for patients with DTC[11–13]. Reoperation may be acceptable for all patients with cervicomediastinal tumour spread[9,14] but contraindicated in those with multiple distant metastases to parenchymatous organs such as the lung and liver[15–18].

This study examined the indications, technical procedure and results of surgical reintervention for DTC, based on data from 110 patients treated between 1986 and 1991.

Patients and methods

Patients

The clinical records and results of postoperative follow-up in 252 patients with a malignant thyroid tumour seen between April 1986 and October 1991 were analysed. The patients had been referred to the University Hospital by endocrinologists, general practitioners or other hospitals.

The distribution of thyroid malignancies is shown in *Table 1*. In patients with DTC the female:male ratio was 4:1 and the mean(s.d.) age 46·6(16·7) (range 11–81) years.

A total of 110 patients underwent reoperation; in 57 (52 per cent) surgery was carried out within 6 months of the first operation. These patients were classified as undergoing a 'completion operation', regardless of whether the thyroid remnant was too large for adequate postoperative radioiodine therapy (25 patients) or whether persistent carcinoma was suspected (32). In 53 patients (48 per cent) reintervention was carried out between 6 months and 22 years after the first operation and was classified as 'operation for recurrent disease'. Ten of these patients had undergone more than one previous operation (up to five) for DTC.

Surgical technique

Surgical intervention was classified as local (32 patients; 29 per cent) when the thyroid tissue and central lymph nodes were removed, and as cervical (66 patients; 60 per cent) when the lateral neck compartment was systematically dissected. Patients undergoing a 'cervicomediastinal' procedure (12 patients; 11 per cent) included those in whom systematic neck dissection was combined with a trans-sternal mediastinal approach.

Table 1 *Histology of malignant thyroid tumours*

Histology	No. of tumours
Differentiated thyroid carcinoma	
First operation	75 (30)
Reoperation	110 (44)
Medullary thyroid carcinoma	47 (19)
Other	20 (8)
Total	252 (100)

Values in parentheses are percentages

Remaining postoperative tumour burden

Only when the serum thyroglobulin level was <5 ng/ml and radioiodine scans and other localization studies negative were patients considered free from tumour. Occult tumours were present in patients with negative localization studies and a thyroglobulin level ≥5 ng/ml. Macroscopic tumour was defined as one positive localization study or as the description of an $R_{1/2}$ resection by the surgeon at the previous operation.

Histology and grading

All specimens were analysed by the Department of Pathology at the University of Düsseldorf. In 38 (72 per cent) of the 53 patients with recurrent DTC the grading of primary and recurrent tumours was available. The grading of the primary tumour into well, moderately or poorly differentiated thyroid carcinoma was compared with the histological grading of recurrent DTC.

Results

Sixty-five (59 per cent) of 110 patients undergoing surgical reintervention for DTC were free from tumour after the operative treatment, the median follow-up being 2·3 years. Thirty-nine (68 per cent) of 57 patients with a 'completion reintervention' and 26 (49 per cent) of 53 with recurrent disease were tumour-free after the treatment (*Table 2*).

When papillary and follicular thyroid carcinomas were assessed separately, 81 per cent of patients with papillary and 52 per cent of those with follicular thyroid carcinoma were found to be free from tumour after operation. Tumour stage, however, differed in the two groups, with a larger number of small and intrathyroid papillary lesions (89 of 133; 67 per cent) than follicular tumours (18 of 52; 35 per cent).

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Table 2 *Tumour status in 110 patients undergoing reoperation for differentiated thyroid carcinoma*

Type of operation	Extent of operation			
	Local	Cervical	Cervical plus mediastinal	Total
Completion	17 of 20 (85)	22 of 37 (59)	0 of 0 (0)	39 of 57 (68)
Recurrent	7 of 12 (58)	16 of 29 (55)	3 of 12 (25)	26 of 53 (49)
Total	24 of 32 (75)	38 of 66 (58)	3 of 12 (25)	65 of 110 (59)

Values are number of patients free from tumour of the total number undergoing that operation, with percentages in parentheses

Table 3 *Results of reoperation in patients with differentiated thyroid carcinoma in relation to tumour stage*

Stage	No. of patients	No tumour after first operation	No tumour after reoperation	Persistent disease	Died
$T_1N_0M_0$	4	3 (75)	1 (25)	0 (0)	0 (0)
$T_{1-3}N_{0/1}M_0$	59	28 (47)	20 (34)	11 (19)	0 (0)
$T_4N_{2/3}M_0$	25	1 (4)	11 (44)	12 (48)	1 (4)
$T_xN_xM_1$	22	0 (0)	1 (5)	14 (64)	7 (32)
Total	110	32 (29)	33 (30)	37 (34)	8 (7)

Values in parentheses are percentages

Of 25 patients who underwent reoperation before radioiodine treatment because of large remnants of normal thyroid tissue, two were found to have occult tumour foci. Nine patients with suspected persistent disease had no tumour and results for postoperative radioiodine uptake and serum thyroglobulin level were negative. Therefore, 32 (29 per cent) of 110 patients who underwent surgical reintervention had already been cured of locoregional tumour spread by the primary operation. Of the remaining 78 patients, 33 (30 per cent) were free from tumour after surgical reintervention and 24 (22 per cent) showed only occult tumour with a raised thyroglobulin level. Twenty-one patients (19 per cent) showed signs of a macroscopically evident persistent tumour after secondary surgery.

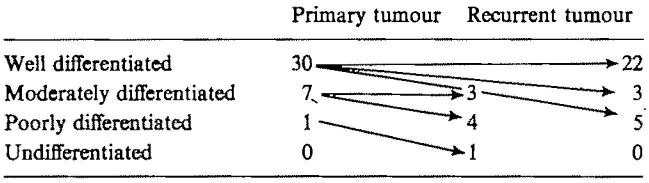
The efficacy of secondary surgery depended largely on the extent of the tumour (*Table 3*). Thirty-one (49 per cent) of 63 patients with small tumours ($T_1N_0M_0$ and $T_{1-3}N_{0/1}M_0$) had been cured by the first operation. Of the remaining 32 patients, 21 were cured by surgical reintervention, the mean follow-up being 2·3 years. In 25 patients with extrathyroid tumour growth (T_4 and/or $N_{2/3}$) involving the lateral neck or the mediastinal compartment, one had already been cured by the first operation and an additional 11 were cleared of tumour by reintervention. Of 22 patients with distant metastases, only one, who is still alive, achieved complete remission by secondary surgery for 2 years.

Of the 45 patients with persistent disease, 37 survived and eight, all of whom showed macroscopic tumour foci after operation, died (*Table 3*).

When the grade of recurrent tumour tissue was compared with that of the primary lesion, histological dedifferentiation was detected in 13 of 38 patients (*Table 4*). No patient with recurrent DTC had a higher grade of differentiation in the recurrent tumour than in the primary lesion. Dedifferentiation of the recurrent tumour was diagnosed in eight of 30 well differentiated, in four of seven moderately differentiated and in one poorly differentiated tumour. Dedifferentiation was seen more often in recurrent tumours from follicular (nine of 18) than from papillary (four of 20) thyroid carcinomas.

There was no 30-day perioperative mortality. Morbidity resulting from surgical reintervention for locally persistent or recurrent disease included a high proportion of recurrent laryngeal nerve paralysis (eight of 110 patients; 7 per cent) and hypoparathyroidism (three of 110; 3 per cent). The eight cases of paralysis, however, included four nerves that had been sacrificed because of tumour infiltration. Accidental nerve damage therefore amounted to 4 per cent. Following neck dissection two chyle leaks closed without further intervention 10 days and 5 weeks after surgery.

Table 4 *Graded differentiation in primary and recurrent differentiated thyroid carcinoma*



	Primary tumour		Recurrent tumour
Well differentiated	30		22
Moderately differentiated	7	3	3
Poorly differentiated	1	4	5
Undifferentiated	0	1	0

Discussion

The prognosis for patients with DTC depends on age and tumour stage[19–24]. Histological grading and tumour ploidy are of some prognostic importance[19,25–28], and the impact of low iodine supplementation has been confirmed[29,30]. The importance of total thyroidectomy and additional neck dissection for younger patients with DTC remains controversial[13,19,23]. Because the efficacy of radical surgery is questioned only for young patients with small papillary thyroid carcinoma[22,23,31], it may be inappropriate to rely on conservative surgery for DTC in all patients[24]. In areas of low natural iodine total thyroidectomy is advocated for all patients of ⩾40 years, for those with primary tumours >1·5 cm in diameter and for DTC with a follicular or follicular–papillary histology[14,27,32,33]. Thyroidectomy should include a systematic compartment dissection in patients with clinically evident lymph node metastases (cervical or mediastinal)[8,11]. Cervical compartment dissection is also indicated for all patients with T_4 tumours. In contrast to the opinion of others[9,28,31], we believe that routine neck dissection may not be necessary in patients without clinically evident extrathyroid disease.

After thyroidectomy all patients in the present study were referred for a whole-body scan with radioiodine. It was therefore logical to perform secondary surgery in patients in whom total thyroidectomy was indicated or who had remnants of normal thyroid tissue to avoid exposure to unnecessarily high doses of radioiodine.

Compared with other studies, the proportion of patients undergoing surgical reintervention appears to be rather high. Fine-needle aspiration cytology before primary surgery is routine practice and surgical strategy is determined accordingly. However, since Germany is an iodine-deficient country with a high incidence of multinodular goitre, aspiration cytology is a less sensitive procedure.

Secondary surgical intervention was indicated in all patients with persistent or recurrent tumour tissue. For all 19 patients with small primary tumours ($T_{1/2}N_{0/1}M_0$) who were aged <40 years, the indication for radioiodine treatment and surgical reintervention is questionable; only four of these 19 patients had follicular thyroid cancer, leaving 15 who were possibly 'overtreated'.

With persistent tumour there is a need for total tumour excision: eight of 21 patients with macroscopic residual tumour died during a mean follow-up of 2·3 years. These patients might well constitute a specific subgroup with a more aggressive tumour (distant metastases were present at the time of reoperation in 19 of the 21 patients), but it is still advisable to achieve total tumour excision to prevent malignant transformation[24,25].

Malignant transformation of DTC into undifferentiated types of carcinoma has been suspected by others[34–36]. In the present series histological signs of transformation were seen in one-third of tumours.

Bäckdahl[37] found identical ploidy patterns in primary and recurrent DTC, and cell cultures with different proliferative activity and growth aggressiveness show no difference in ploidy pattern[38]. The validity of ploidy in the interpretation of tumour behaviour remains doubtful[39]. Ploidy in papillary thyroid cancer has been used to decide whether or not therapy should be aggressive[40]. The polyclonal nature of tumours[41,42], however, might reduce the reliability of ploidy studies.

Surgical reintervention is advocated in persistent and recurrent DTC[6,9,10,18]. In the present study total tumour relief was achieved in 47 per cent of patients with proven disease undergoing early reintervention, and in 49 per cent of those undergoing reintervention 6 months to 22 years after the first operation. The value of early diagnosis and reintervention in persistent and recurrent tumour disease has not been demonstrated[7].

Auguste and Attie[14] reported no cases of laryngeal nerve paralysis after completion thyroidectomy. The present study revealed accidental paralysis in 4 per cent of patients. The data might not be directly comparable, however, as 50 per cent of the present patients who suffered paralysis had locally advanced ($T_{2-4}N_{2/3}$) disease. A complication-free operation seems an unrealistic aim. Complications following neck dissection and trans-sternal–mediastinal dissection were low, with one paralysis of the accessory and one of the phrenic nerve. Two chyle leaks closed without further intervention. Attie[6] did not see any of these problems in over 300 patients undergoing neck dissection.

In summary, successful surgical reintervention was observed in 59 per cent of all patients showing total tumour relief. In 22 per cent of patients tumour was reduced to occult persistent disease. The complication rate was low and therefore surgical reintervention should be advocated when no distant metastases are evident for patients with locoregional and mediastinal DTC.

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Case report

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Small bowel obstruction caused by recurrent cystic lymphangioma

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Intra-abdominal cystic lymphangiomas are rare tumours that can occur in the omentum, retroperitoneum and the mesentery or wall of the small or large bowel. They are thought to be congenital in origin and most do not give rise to symptoms, being discovered incidentally at laparotomy or autopsy. Symptoms usually result from compression of intra-abdominal viscera. A case is presented of recurrent cystic lymphangioma causing small bowel obstruction 24 years after initial resection.

Case report

A 47-year-old woman was admitted as an emergency with a 6-h history of colicky paraumbilical pain and vomiting. Some 24 years earlier she had undergone laparotomy for lower abdominal peritonism, at which a haemorrhagic ovarian cyst and a mass within the mesentery of the ileum were found. The ovarian cyst and the mesenteric mass together with a corresponding segment of the ileum were resected. Histological examination of the resected specimen showed a benign haemorrhagic ovarian cyst and a mesenteric cystic lymphangioma.

Examination revealed tachycardia, abdominal distension and marked tenderness in the paraumbilical region. Bowel sounds were increased. A provisional diagnosis of intestinal obstruction was made. Investigation revealed leucocytosis ($16{\cdot}5 \times 10^9$ cells/l). Platelet count, and levels of haemoglobin, electrolytes and serum amylase were normal. Abdominal radiography showed dilated loops of small bowel consistent with obstruction.

At laparotomy the anastomosis from the previous resection was identified 15 cm from the ileocaecal junction. The small bowel was oedematous and thickened from about 30 cm proximal to the anastomosis down to the caecum. The corresponding mesentery was similarly oedematous and thickened. The proximal small intestine was dilated but otherwise normal. The entire length of oedematous small bowel and the caecum was excised together with the corresponding mesentery. A one-layer end-to-end anastomosis was performed. The patient made an uneventful recovery.

Histological examination of the resected small bowel showed large dilated lymphatics lined by a row of flattened endothelial cells within the mesentery and submucosa of the small bowel. Aggregates of lymphoid tissue were seen in close relationship to the dilated lymphatics. These histological changes were identical with those seen after the previous small bowel resection, confirming a recurrence of cystic lymphangioma.

Discussion

The aetiology of lymphangioma is uncertain. Wegener[1] classified such tumours into three types: simple capillary, cavernous and cystic. Cystic lymphangiomas are composed of one or more cysts (lined by endothelium) ranging from 0·1 to 5 cm in diameter and often communicating with each other. In the mesentery they often contain chyle. These tumours are not encapsulated. They are frequently incidental findings but have been known to cause intestinal obstruction[2]. Computed tomography may prove helpful in diagnosis[3]. Complete excision is the treatment of choice[4]; incomplete removal, as in the present patient, resulted in recurrence 24 years later.

Acknowledgements

The authors thank Mr R. J. Cuschieri for allowing them to report this patient.

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Short note

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Polytetrafluoroethylene patch grafting for closure of stomach defects in the rat

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Definitive surgical management of large lacerations of the second and third parts of the duodenum and of chronic duodenal fistula and perforation resulting from malignant infiltration of the stomach and duodenum is difficult[1–4].

To solve these problems, the serosal patch technique[1,5], pedicle patches of ileum, and lyophilized bovine tendon-like heterologous structures have been employed[2]. However, use of an expanded polytetrafluoroethylene (PTFE) patch (GORE-TEX; W. L. Gore, Elkton, Arizona, USA) for this purpose has not been cited in the literature. In the present study, the healing process of experimental stomach defects closed by a PTFE patch was followed.

Materials and methods

Fourteen 8-week-old male rats (*Rattus norvegicus albus*) weighing 200 g were used. Each was given standard feed and water, and starved for 8 h before the experiments.

Under ether anaesthesia a midline laparotomy was made and a defect 1 cm in diameter in the fundus area of the stomach created by removing the full thickness of the gastric wall. This defect was then closed with a PTFE patch, secured with a continuous 3/0 polypropylene suture taken from the seromuscular layer and placed within 1 mm of the edge of the graft. After haemostasis had been achieved, the abdomen was closed without drainage using 2/0 nylon.

Rats were allowed water within the first 24 h after operation; standard feeding was resumed after this. No antibiotics were given. The animals were killed at 3, 5, 8, 14, 20 and 30 days.

The grafted area with surrounding healthy tissue was excised from the dead rats and fixed in 10 per cent neutral formaldehyde. The excised tissue was placed in paraffin blocks and 6-μm sections taken for routine histological examination following staining with haematoxylin and eosin.

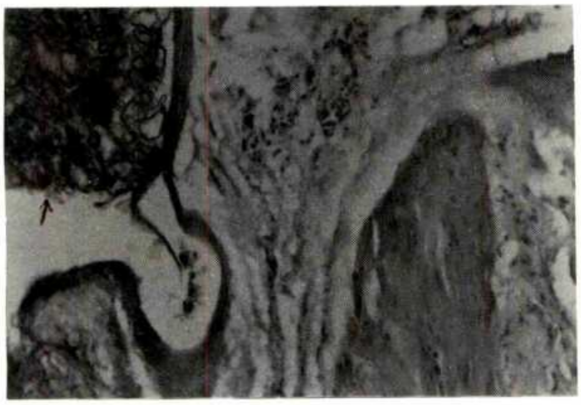

Figure 1 *Day 3. The central portion of the graft remains bare. The section shows new tissue proliferation from the healthy region to the grafted area (arrow). (Haematoxylin and eosin stain, original magnification ×64)*

Results

Two rats died within 48 h. At autopsy, none of the animals showed any evidence of leakage or peritonitis. There were no adhesions in the area of the patch or elsewhere in the abdominal cavity.

Histological examination showed progressive covering of the graft with cellular material, starting from the edges and eventually covering the whole area of the graft with keratinized squamous epithelium (*Figures 1–6*).

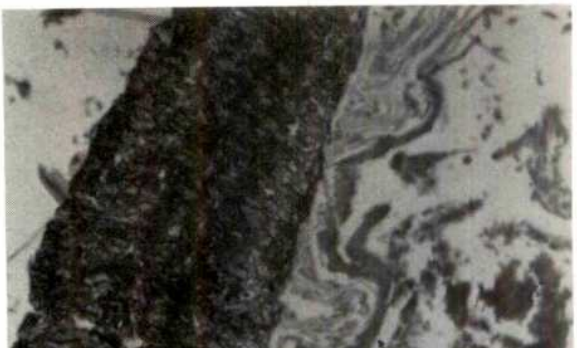

Figure 2 *Day 5. The graft is covered with cellular material on the luminal surface. Epithelialization has begun and a massive polymorphonuclear cell infiltrate is present. (Haematoxylin and eosin stain, original magnification ×32)*

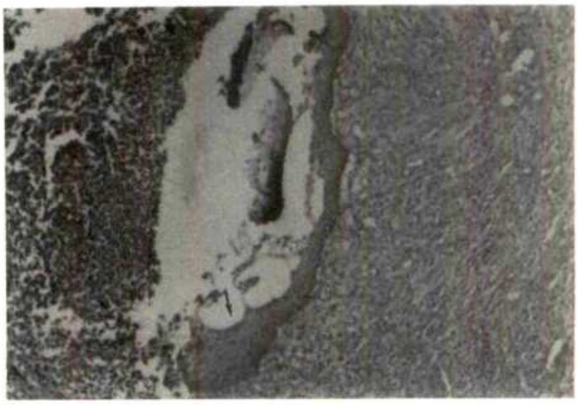

Figure 3 *Day 8. Continuation of polymorphonuclear cell infiltration, with deposition of collagen and growth of stratified squamous epithelium. (Haematoxylin and eosin stain, original magnification ×128)*

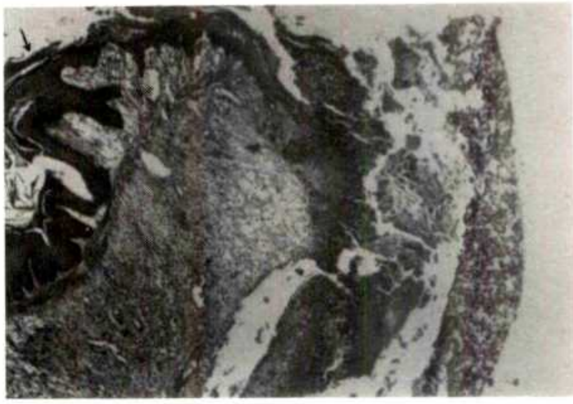

Figure 4 *Day 14. Keratinization (arrow) with formation of glands and muscle in the connective tissue. There is continuing polymorphonuclear cell infiltration. (Haematoxylin and eosin stain, original magnification ×64)*

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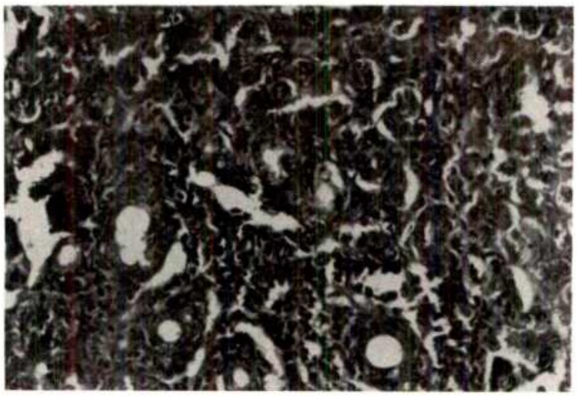

Figure 5 *Day 20. Eosinophil infiltration, proliferation of gland and muscle structures. Progression of squamous epithelium is observed, with a reduction in polymorphonuclear cell infiltration. (Haematoxylin and eosin stain, original magnification × 64)*

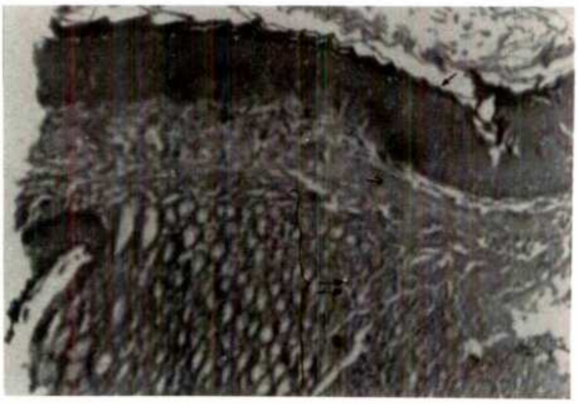

Figure 6 *Day 30. Stratified squamous keratinizing epithelium (single arrows), gland (double arrow), muscle and connective tissue: a typical stomach wall structure overlying the polytetrafluoroethylene graft. Polymorphonuclear cell infiltration has greatly reduced. (Haematoxylin and eosin stain, original magnification × 32)*

Discussion

PTFE is chemically inert, highly electronegative and hydrophobic. This prosthesis was first used clinically in a vascular procedure[6] in 1972. The present study shows that a PTFE patch is easy and reliable to use for grafting of stomach defects. None of the rats showed evidence of leakage or peritonitis.

The regeneration of tissue, which started from the third day after operation, had resulted in the formation of a typical stomach wall structure by the end of a 1-month period. The fundic area of a healthy rat is normally covered by columnar epithelium[7]. In the present study the newly formed tissue differed from this original tissue only by containing stratified squamous keratinizing epithelium.

Based on the results of these preliminary studies, we believe the technique can be used with ease and reliability. However, further work using a more appropriate animal model is required before patch grafting with PTFE for this kind of surgery can be applied to humans.

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Prognostic relevance of systematic lymph node dissection in gastric carcinoma

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In a prospective multicentre study of 2394 patients with gastric carcinoma the prognostic relevance of systematic lymph node dissection was evaluated. Of 1654 patients undergoing resection, 558 had a standard lymph node dissection, defined as fewer than 26 nodes in the specimen, and 1096 underwent radical lymphadenectomy, i.e. 26 or more nodes in the specimen. Radical dissection significantly improved the survival rate in patients with Union Internacional Contra la Cancrum (UICC) stages II and IIIA tumours. Multivariate analysis identified radical dissection as an independent prognostic factor in the subgroups of patients with UICC tumour stages II and IIIA. Radical dissection conferred no survival advantage in patients with pN_2 *tumours. There was no significant difference in morbidity and mortality rates between radical and standard lymph node dissection. Radical lymphadenectomy improves survival in patients with UICC gastric cancer stages II and IIIA, and should be the recommended treatment for such patients.*

Systematic lymph node dissection makes the surgical therapy of gastric carcinoma more radical and aims to increase the likelihood of complete tumour excision. Complete locoregional tumour removal with adequate margins of clearance, i.e. R_0 resection according to the Union Internacional Contra la Cancrum (UICC) 1987 classification[1] (UICC R_0) or absolute R_0 resection[2], is the most important factor in reducing locoregional tumour recurrence and may improve survival time. Extended resection should be of benefit for patients in whom UICC R_0 can be achieved only by this approach and adequate lymph node staging can be performed only after radical lymphadenectomy. Reliable tumour staging is a prerequisite for a scientific approach to the problem of gastric cancer. The prognostic value of systematic lymphadenectomy was assessed using the data of the prospectively conducted German Gastric Carcinoma Study.

Patients and methods

The prospective multicentre study included all patients with gastric carcinoma admitted to one of 19 participating university hospitals in Germany or Austria. Details of the surgical procedure, histopathological parameters of the tumour and follow-up were documented prospectively from 1986 to 1989 at the individual centres (*Table 1*). Data were posted to a registry immediately after collection and follow-up was performed at individual hospitals or by the patients' physician in cooperation with the hospital. Survival time was used as the endpoint of the analysis. The mean follow-up of all surviving patients was 48 months; follow-up was complete for 99·2 per cent of the enrolled patients.

Before the study, several 'consensus meetings' of the involved surgical centres were organized to standardize resection techniques and terminology. Lymph node dissection was demonstrated and taught according to the recommendations of the Japanese Research Society for Gastric Cancer[5]. Teaching videos were made available to all participating surgeons. The departments of surgery of the Technische Universität München and Medizinische Hochschule Hannover served as surgical reference centres for at least one obligatory practical training course.

En bloc resection with removal of group 1 and 2 lymph nodes was recommended as the surgical procedure of choice. Group 1 comprises all nodes along the major and minor curvatures of the stomach, i.e. lymph node stations 1–6 in patients undergoing total gastrectomy and 3–6 in those submitted to subtotal gastrectomy[5]. Group 2 comprises lymph node stations 7–12 in the Japanese classification[5]. Dissection of group 2 nodes was performed as described previously[6].

Although all surgeons agreed to perform dissection of group 1 and 2 nodes, removal of group 1 nodes only was performed as the standard procedure in some of the participating centres. This was demonstrated objectively by a careful assessment of the removed nodes. Histopathological examination by the participating pathologists, who had agreed to a uniform assessment and documentation of the specimen, thus served as a quality control of the extent of lymphadenectomy. This provided the opportunity to compare the results of more and less extensive lymph node dissections in patients with gastric carcinoma.

Patient population

A total of 2394 patients with gastric carcinoma were seen at the participating hospitals during the study period. A group of 255 were excluded because of previous radiation or chemotherapy, previous gastric resection, second malignancy or because gastric carcinoma was not confirmed histologically. Another 140 patients were excluded because histopathological assessment was not complete. Data from the remaining 1999 patients were analysed; resection was performed in 1654 (82·7 per cent). Demographic data and tumour characteristics of these are shown in *Table 2*.

The extent of gastric resection was determined by tumour type (Laurén[3] classification) and location of the lesion. Total gastrectomy was the standard procedure (n = 787; 47·6 per cent). In patients with

Table 1 *Summary of details recorded for prospective patient documentation*

Surgery	Pathology
Demographic data	Tumour size and site
Blood tests	Laurén[3] classification
Risk factors	Borrmann[4] classification
Concomitant disease	Grading
Diagnostic findings	pTNM category
Intraoperative findings	Lymph node count
Extent of resection	UICC $R_{0/1}$ classification
Type of reconstruction	
Residual tumour	
Postoperative course	
Follow-up	

TNM, tumour node metastasis; UICC, Union Internacional Contra la Cancrum

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Table 2 *Patient and tumour characteristics for all 1654 patients undergoing resection and 1182 receiving UICC R_0 resection*

	No. of patients undergoing resection			No. of patients undergoing UICC R_0 resection	
	Total ($n = 1654$)	Standard dissection (≤25 nodes; $n = 558$)	Radical dissection (>25 nodes; $n = 1096$)	Standard dissection (≤25 nodes; $n = 379$)	Radical dissection (>25 nodes; $n = 803$)
Mean(s.d.) age (years)	62·5(12·0)	64·1(12·5)	62·0(11·9)	64·0(12·5)	61·8(11·6)
Sex ratio (M:F)*	1048:606 (63·4:36·6)	374:184 (67·0:33·0)	674:422 (61·5:38·5)	264:115 (69·7:30·3)	505:298 (62·9:37·1)
Karnofsky index ≥70%*	1575 (95·2)	521 (93·4)	1056 (96·4)	358 (94·5)	776 (96·6)
Tumour site*					
Proximal third	496 (30·0)	172 (30·8)	324 (29·6)	120 (31·7)	242 (30·1)
Middle third	643 (38·9)	194 (34·8)	449 (41·0)	131 (34·6)	335 (41·7)
Distal third	435 (26·3)	175 (31·4)	260 (23·7)	126 (33·2)	209 (26·0)
Entire stomach	80 (4·8)	17 (3·0)	63 (5·7)	2 (0·5)	17 (2·1)
Borrmann classification I or II ($n = 1371$)*	576 (42·0)	197 (44·6)	379 (40·8)	131 (48·9)	296 (46·3)
Laurén intestinal type*	858 (51·9)	313 (56·1)	545 (49·7)	227 (59·9)	416 (51·8)
UICC stage*					
IA	229 (13·8)	99 (17·7)	130 (11·9)	96 (25·3)	130 (16·2)
IB	221 (13·4)	84 (15·1)	137 (12·5)	77 (20·3)	133 (16·6)
II	230 (13·9)	89 (15·9)	141 (12·9)	76 (20·1)	129 (16·1)
IIIA	262 (15·8)	85 (15·2)	177 (16·1)	66 (17·4)	145 (18·1)
IIIB	204 (12·3)	44 (7·9)	160 (14·6)	30 (7·9)	130 (16·2)
IV	508 (30·7)	157 (28·1)	351 (32·0)	34 (9·0)	136 (16·9)

*Values in parentheses are percentages. UICC, Union Internacional Contra la Cancrum

locally advanced tumours of the proximal or middle third of the stomach resection was extended to the distal oesophagus or tail of the pancreas ($n = 389$; 23·5 per cent). Patients with small intestinal-type gastric carcinoma located in the distal third of the stomach underwent subtotal four-fifths gastric resection ($n = 382$; 23·1 per cent). Proximal gastrectomy was performed on 96 patients (5·8 per cent).

Extent of lymph node dissection

Anatomical investigations have shown that an average of 27 lymph nodes can be expected in the specimen when systematic dissection of group 1 and 2 nodes is performed[7]. Based on this observation and the results of histopathological examination of the resected specimen in the present study, removal of 26 or more nodes was defined as radical lymphadenectomy[5]. Extirpation of fewer than 26 nodes was defined as standard lymphadenectomy[5]. Of the 1654 patients undergoing resection, 558 had a standard and 1096 a radical dissection.

An overall mean(s.d.) of 35·3(20·4) (median 33) lymph nodes were removed with the specimen. There was a mean(s.d.) of 15·4(6·9) (median 16) removed lymph nodes in patients who underwent standard dissection, while the radical procedure resulted in removal of a mean(s.d.) of 45·4(17·2) (median 41) nodes. Survival data and morbidity and mortality rates were compared between these two groups.

Statistical analysis

Survival curves and confidence intervals were calculated according to Kaplan and Meier[8] and Brookmeyer and Crowley[9] respectively. Survival data are given as observed overall survival and include postoperative mortality. The log rank test[10] was used to assess statistical differences between groups.

The potentially prognostic factors shown in *Table 1* were assessed by multiple stepwise regression analysis using a Cox[11] model for patients with stages II and IIIA tumours. Significance was determined by χ^2 analysis.

The entire statistical assessment was performed using the BMDP package (BMDP Statistical Software, Los Angeles, California, USA).

Survival curves were calculated for the entire patient population and those who, based on clinical, surgical and histopathological evaluation, underwent UICC R_0 resection[1]. Separate analysis of patients who underwent R_0 resection appeared reasonable, since this resection was one of the strongest prognostic factors on multivariate analysis.

Results

The distribution of demographic data and UICC tumour stage did not differ between patients who underwent standard and

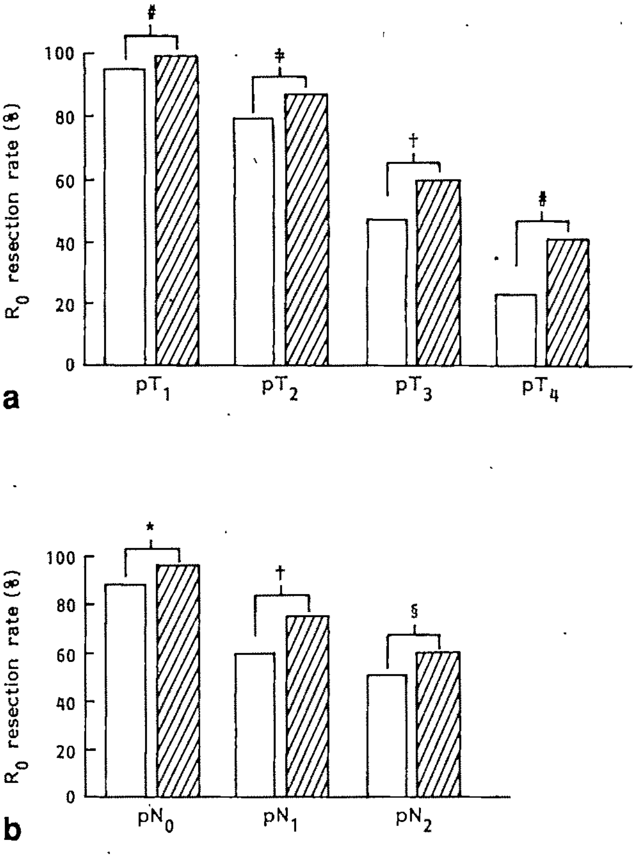

Figure 1 *Frequency of Union Internacional Contra la Cancrum (UICC) R_0 resection in patients undergoing standard (□) or radical (■) lymph node dissection in relation to* **a** *pT and* **b** *pN category. pT_1, invasion of lamina propria or submucosa; pT_2, invasion of muscularis propria or subserosa; pT_3, invasion of serosa; pT_4, infiltration of contiguous structures. pN_0, no regional lymph node metastases; pN_1, lymph node metastases ≤3 cm from margins of the primary tumour; pN_2, lymph node metastases >3 cm from margins of the primary tumour or to nodes of the left gastric artery, common hepatic artery, splenic artery or coeliac axis.* *P = *0·002;* †P = *0·003;* ‡P = *0·01;* §P = *0·02;* ♯P *not significant* (χ^2 *test*)

those who had radical lymph node dissection. The prevalence of lymph node metastases was not dependent on the number of lymph nodes dissected provided 15 or more nodes were removed.

Multivariate analysis identified R_0 resection, i.e. complete macroscopic and microscopic tumour removal, as one of the strongest independent prognostic factors. Of the 1654 patients undergoing resection, 1182 met the criteria for an R_0 procedure, a rate of 71·5 per cent. Demographic and histopathological data of patients who underwent UICC R_0 resection are given in *Table 2*.

When analysed according to the UICC pT and pN category[1], radical dissection significantly increased the rate of R_0 resection in patients with pT_2, pT_3 or pT_4 tumours and those with pN_0, pN_1 or pN_2 lymph node status (*Figure 1*). Consequently, radical dissection resulted in a significantly increased rate of R_0 resection for all UICC stages. This was associated with a significantly increased survival rate in patients with UICC stage II or IIIA disease (*Table 3; Figure 2*). On multivariate analysis radical dissection had an independent prognostic impact on survival rate in patients with tumour stages II ($P < 0{\cdot}001$) and IIIA ($P < 0{\cdot}05$). Radical dissection conferred no survival advantage over standard lymphadenectomy in patients with UICC tumour stage IA or IB, nor in those with pN_2 lymph node status or distant metastases (i.e. UICC stages IIIB and IV).

There was no difference in morbidity and 30- or 90-day mortality rates between the two types of lymph node dissection (*Table 4*).

Table 3 *Survival according to UICC stage and number of lymph nodes removed in patients undergoing UICC R_0 resection*

UICC stage	Type of lymph node dissection	Median (95% c.i.) survival time (months)	5-year survival rate(s.d.) (%)	P*
IA	Radical (n=130)	—	85·7(3·1)	0·18
	Standard (n=96)	—	86·5(3·7)	
IB	Radical (n=133)	—	68·7(5·1)	0·2
	Standard (n=77)	—	72·4(5·7)	
II	Radical (n=129)	—	55·2(5·1)	<0·001
	Standard (n=76)	25·6 (19·8–31·9)	26·8(6·0)	
IIIA	Radical (n=145)	28·9 (22·8–40·1)	38·4(4·3)	0·03
	Standard (n=66)	14·3 (10·1–29·0)	25·3(7·5)	
IIIB	Radical (n=130)	15·5 (12·4–19·7)	17·5(4·0)	0·36
	Standard (n=30)	12·2 (9·9–17·4)	27·5(8·7)	
IV	Radical (n=136)	12·5 (9·8–15·3)	16·1(3·5)	0·13
	Standard (n=34)	16·1 (10·0–24·4)	28·2(7·5)	

UICC, Union Internacional Contra la Cancrum; c.i., Brookmeyer–Crowley confidence interval. *Log rank test

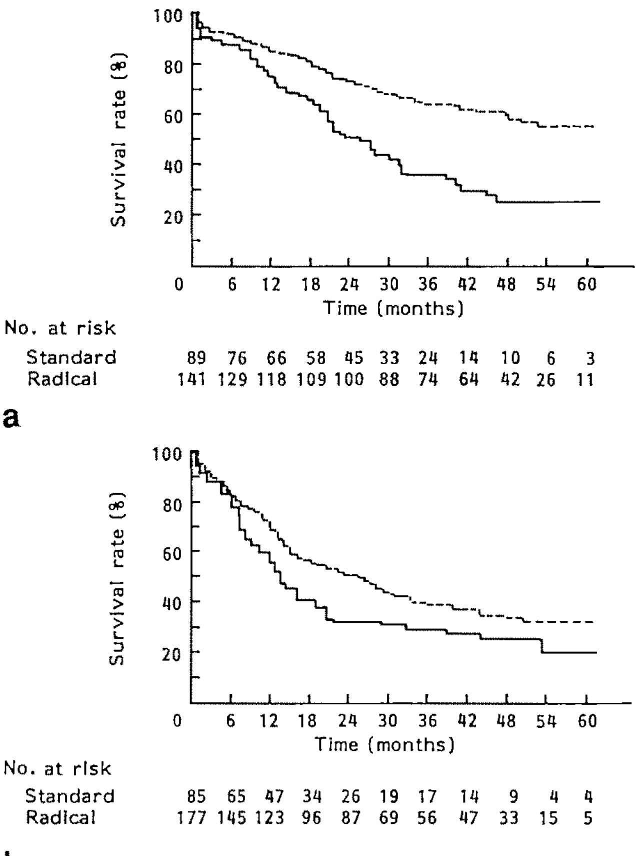

Figure 2 *Survival rates for patients with Union Internacional Contra la Cancrum* **a** *stage II* ($P < 0{\cdot}001$) *or* **b** *stage IIIA* ($P = 0{\cdot}02$) *gastric carcinoma undergoing standard (——) or radical (----) lymph node dissection. Comparisons are made using the log rank test*

Discussion

To obtain data to answer the questions posed by the present study objectively it was necessary to analyse a large number of patients treated in a standardized fashion over a defined period of time as a multicentre trial. Inconsistencies usually associated with such a multicentre trial were minimized by a series of consensus meetings. Data collected in this study may therefore be more pertinent than those reported from a single centre with a limited number of patients treated inconsistently over periods of 10 or more years.

As a consequence of the lack of a good and practical definition of the extent of lymph node dissection in the literature[5], the definition in the present study was made according to anatomical investigations[7]. Removal of 26 or more

Table 4 *Morbidity and mortality rates of standard* versus *radical lymph node dissection*

	Total		UICC stage											
			IA		IB		II		IIIA		IIIB		IV	
	Standard (n=558)	Radical (n=1096)	Standard (n=99)	Radical (n=130)	Standard (n=84)	Radical (n=137)	Standard (n=89)	Radical (n=141)	Standard (n=85)	Radical (n=177)	Standard (n=44)	Radical (n=160)	Standard (n=157)	Radical (n=351)
Type of complication														
Suture insufficiency	8·2	8·0	4	5·4	10	5·8	12	9·2	8	8·5	11	8·8	7·0	8·8
Bleeding	1·8	1·9	2	0·0	2	1·5	1	3·5	0	1·1	5	2·5	1·9	2·3
Wound healing	3·9	3·8	4	4·6	7	2·2	8	3·5	1	6·8	2	3·1	1·9	3·1
Abscess	3·2	4·7	3	5·4	4	4·4	1	2·8	5	5·1	9	7·5	1·9	4·0
Cardiopulmonary	9·5	9·3	10	8·5	7	10·2	14	12·8	9	8·5	5	6·3	9·6	9·7
Other	2·3	2·7	1	3·8	2	1·5	1	2·8	2	2·8	2	2·5	3·8	2·8
Total rate	29·0	30·6	24	27·7	32	25·5	37	34·8	26	32·8	34	30·6	26·1	30·8
Mortality rate														
30-day	5·2	5·0	3	3·1	5	2·9	7	5·0	4	6·8	5	4·4	7·0	6·0
90-day	10·0	10·9	3	5·4	7	5·8	9	7·1	12	9·0	7	10·6	16·6	17·4

Values are percentages UICC, Union Internacional Contra la Cancrum lymph nodes was defined as complete or radical lymphadenectomy corresponding to the R_2 resection of the Japanese nomenclature[5]. Removal or fewer than 26 nodes was defined as standard lymph node dissection, corresponding to the Japanese R_1 procedure[5]. Evaluation of the number of lymph nodes removed thus served as an objective quality control of the extent of lymphadenectomy.

In the present study multivariate analysis identified UICC R_0 resection[1], i.e. the absence of residual tumour after resection, as the strongest prognostic factor for survival. Compared with standard lymphadenectomy, radical dissection increased the rate of UICC R_0 resection[1] and significantly improved survival, particularly in patients with disease of stage II or IIIA.

A comparable improvement in the prognosis of patients with gastric carcinoma receiving radical dissection has been demonstrated in the studies of Mine *et al.*[12], Shiu and associates[13] and Jaehne and co-workers[14]. The present study is, however, the first to show that radical dissection can improve survival in prospectively documented patients with gastric carcinoma of UICC stage II or IIIA. This effect was, however, present only in patients with UICC pN_0 or pN_1 disease. This result suggests that the effect may result from the increased rate of complete local tumour removal (UICC R_0 resection). In the present study about 50 per cent of patients, i.e. all those with pN_0 or pN_1 disease[1], might have benefited from radical dissection. Radical lymphadenectomy certainly can improve survival in patients within the pN_1 category[1] (17·1 per cent of the present patients undergoing resection).

Since a more radical nodal dissection may also allow more accurate staging, radical lymphadenectomy might result in a higher prevalence of patients with lymph node metastases, thus biasing the present results. The study showed that the prevalence of patients with lymph node metastases did not depend on the number dissected provided 15 or more nodes were removed. Similar data have been reported in patients with carcinoma of the breast[15] or colon[16]. The present mean of 15·4 removed lymph nodes in patients who underwent standard node dissection and the similar distribution of tumour stage in those who had a standard or radical lymphadenectomy therefore suggest that the observed differences in survival rate do not result from differences in the distribution of tumour stage or understaging of the extent of disease in patients who underwent the standard procedure.

The report by Dent *et al.*[17] and preliminary results from prospective studies in the Netherlands[18] and the UK[19] showed an increased morbidity and mortality rate associated with radical lymph node dissection. In the present study the morbidity and mortality rates were similar with the two dissection procedures. This is in accordance with the experience of the Memorial Sloan–Kettering Cancer Center, New York[13,20], and the National Cancer Centre, Tokyo[21,22]. The experience of the surgeon and his or her personal attitude towards lymph node dissection may influence the morbidity associated with the procedure. The present study allowed surgeons at each centre to perform their preferred procedure. This may be of importance in minimizing the surgical complications of radical dissection.

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Effects of tumour necrosis factor on protein metabolism

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Increased skeletal muscle breakdown and negative nitrogen balance are features of sepsis that may be mediated by cytokines. The effects of tumour necrosis factor (TNF) on protein metabolism were studied. When administered to anaesthetized dogs ($0{\cdot}57 \times 10^5$ units per kg body-weight over 6 h), TNF caused urinary nitrogen excretion to increase (mean(s.e.m.) 165(15) mg kg^{-1} for dogs that received TNF versus *113(8) mg kg^{-1} for control animals,* $P < 0{\cdot}01$*). Amino acid nitrogen release from the hindlimbs showed no change over the study period, indicating that the additional urinary nitrogen was not derived from peripheral protein stores. In a second study the same dose of TNF or saline was infused after the intestine had been removed. The mean(s.e.m.) urinary nitrogen excretion in control dogs that had undergone enterectomy (101(7) mg kg^{-1}) was similar to that of intact animals, and addition of TNF did not significantly increase nitrogen excretion (86(18) mg kg^{-1}). The results suggest that nitrogen excreted in the urine during administration of TNF is derived, at least initially, from the intestinal tract.*

Sepsis is associated with increased skeletal muscle protein breakdown and negative nitrogen balance[1]. Amino acids released from the periphery are transported to visceral organs where they are used to provide energy[2], to synthesize acute-phase proteins and to provide carbon skeletons for gluconeogenesis[3]. The nitrogen residue liberated in the liver is converted to urea and excreted in the urine. For many years the intestine was viewed as a quiescent participant in these changes but this view has now been challenged[4]. The gut shows a marked increase in glutamine consumption and an increased release of the key gluconeogenic precursor, alanine, in catabolic states; it is now thought to play an active role in the regulation of interorgan substrate flux.

The metabolic signals that initiate and control these changes are not well understood. Glucagon, catecholamines and glucocorticoids (the 'stress hormones') have previously been implicated[5] but the polypeptide cell products of lymphocytes and macrophages known as cytokines must also now be considered[6]. One cytokine, tumour necrosis factor (TNF), has received much attention because it is able to reproduce many features of sepsis and endotoxaemia[7,8].

The administration of cytokines and the ability selectively to inhibit their effects is steadily increasing. It is hoped eventually that the outlook for critically ill patients will be improved by inhibiting the deleterious effects of cytokines while leaving other beneficial and possibly vital effects intact. It is therefore essential that the mechanisms by which cytokines influence metabolic change are understood. The purpose of the present study was to determine the effect of TNF on urinary nitrogen excretion and to examine the possible contributions to any changes in nitrogen excretion made by the peripheral tissues and the intestine. This is important, as protein breakdown in the intestine may indicate a disruption of this organ with an associated decrease in its barrier function.

Materials and methods

Study 1

Dogs ($n = 24$) of either sex were obtained at least 1 week before the study and housed in accordance with the guidelines of the Committee on Care and Use of Laboratory Animals of the Insitute for Laboratory Animal Resources[9]. Each morning the animals were fed Agway Canine 2000 chow (Agway, Syracuse, New York, USA) and studied only if they were eating normally, maintaining or gaining weight, were afebrile and appeared healthy.

On the morning after an overnight fast of at least 13 h the animals were anaesthetized with pentobarbitone (30 mg per kg body-weight) and intubated. The dogs spontaneously breathed oxygen-enriched room air. Supplementary doses of pentobarbitone were administered as required to maintain light anaesthesia. After catheterization of the urinary bladder and placement of a rectal temperature probe (Yellow Springs Instruments, Yellow Springs, Ohio, USA) the operative areas were shaved and cleaned with povidone–iodine. Using an aseptic technique, a Silastic (Dow Corning, Midland, Michigan, USA) cannula (external diameter 2·16 mm) was placed in the common carotid artery for arterial sampling and pressure monitoring. A similar cannula was also placed in the ipsilateral jugular vein for the infusion of saline and TNF. A balloon-tipped Swan–Ganz catheter was inserted into the pulmonary artery via the same vein; this was used to measure pulmonary artery and wedge pressures and to obtain samples of mixed venous blood.

Approximately 45 min after induction of anaesthesia an infusion of 0·9 per cent saline was commenced via the jugular venous catheter.

In 12 of the 24 dogs (six control, six TNF), cannulas were then placed bilaterally in the groin vessels for the measurement of hindlimb flow and substrate flux, as previously described[10]. Surgical preparation of the groin was complete within 1 h. After operative preparation all animals were left undisturbed for at least 1 h to stabilize before the 6-h infusion began.

At the start of the infusion period, the bladder was emptied by compression and a 6-h urine collection started. At time 0, a sublethal[8] infusion of human recombinant TNF (Asahi Chemical Industry, New York, USA) was administered at a dose of $0{\cdot}57 \times 10^5$ units per kg body-weight, infused at a constant rate over 6 h to animals selected by randomization to groups of equal size. Control animals received an infusion of saline at the same rate. All dogs received a total of 4 ml saline per h per kg body-weight throughout the study.

For all animals undergoing hindlimb flux studies, the hindlimbs were removed and weighed. At the end of the study the skin was divided in a line passing from the pubis, along the inguinal ligament, to the ilium and then extending posteriorly and inferiorly to the ischial tuberosity before returning to the pubis. The hindlimbs were then separated from the trunk and weighed (perineal and pudendal tissues were excluded). The skin and subcutaneous fat was removed and weighed. Finally the muscle was dissected away and the remaining bones and cartilage weighed. Muscle weight was calculated by subtraction.

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Study 2

A further ten dogs were prepared initially as described above, but the operative procedures used were different. Skin preparation was extended to include the perineum, and after the rectum had been emptied the anus was closed with a suture. The temperature probe was inserted into the oesophagus. Before skin incision, 250 mg metronidazole and 250 mg ceftizoxime were administered intravenously as prophylactic antibiotics during intestinal resection.

The abdomen was opened through a lower midline incision. The duodenum was divided approximately at the midpoint of the second part, distal to the entry of pancreatic and biliary ducts. The duodenal stump was closed. A Foley catheter was placed into the stomach via a gastrotomy and secured in place with two purse-string sutures; this ensured gastric drainage and pancreatobiliary decompression. The mesentery of small and large bowel was divided and the vessels ligated. The bowel was divided approximately 25 cm above the pelvic brim. The excised segment was weighed and discarded and the distal stump covered with a glove, which was tied securely in place. The anorectum was then excised through a perianal incision, with dissection close to the bowel wall. After achieving haemostasis the abdomen was closed in a single layer, the gastrostomy tube being brought out through the upper end of the wound. The perineal wound was loosely packed but not sutured. Care was taken to avoid contamination of the peritoneal cavity during the enterectomy. No groin cannulas were inserted in these ten animals.

The time at completion of the procedure was designated as $t = -2$ h. Over the next 2 h the animals were given fluid at a rate of 16 ml kg^{-1} h^{-1}. At $t = 0$ the rate was reduced to 4 ml kg^{-1} h^{-1}. Animals were then randomized to receive saline ($n = 4$) or TNF ($n = 6$; 0·57 × 10^5 units per kg body-weight).

All animals undergoing hindlimb flux studies and all those whose intestine had been removed were killed at the end of the procedure with an overdose of pentobarbitone. The other 12 animals were allowed to recover; when they appeared to be healthy and eating normally (a period of at least 7 days) they were used in other studies, after which they too were killed, in the same manner.

Monitoring and blood sampling

The mean arterial pressure and heart rate were measured at 30-min intervals using a standard mercury manometer. Core body temperature was recorded at half-hourly intervals. Before the start of infusion, at the midpoint and at the end of the study, the rate of oxygen consumption was measured by attaching the dog's endotracheal tube to an oxygen-filled 13·5-litre respirometer (Warren E. Collins, Braintree, Massachusetts, USA) for a period of 4 min.

Blood samples were drawn at predetermined time points. In animals with groin catheters, blood flow was measured at 0, 3 and 6 h in both hindlimbs using an established dye dilution technique[11]; after insertion of the groin catheters an infusion of 0·5 per cent (w/v) *p*-aminohippurate (PAH; Merck, Sharp and Dohme, West Point, Pennsylvania, USA) was delivered through both femoral arterial cannulas at a rate of 0·36 ml min^{-1}. After at least 1 h of PAH infusion and at other designated time points, heparinized blood samples were drawn simultaneously from the carotid artery and both femoral veins, at a rate not exceeding 1 ml every 10 s. At each sampling time three sets of blood samples were drawn at approximately 5-min intervals.

Sample processing

The whole-blood PAH level was measured spectrophotometrically. Glutamine and glutamate concentrations were determined in whole blood using high-performance liquid chromatography[12]. Other amino acid concentrations were determined using a Beckmann Amino Acid Analyzer 6300 (Beckmann Instruments, Brea, California, USA). Standard clinical laboratory techniques were used to measure pH, values being corrected to the core body temperature of the animal at the time of sampling. Urine ammonia was estimated by allowing dissolved ammonia to diffuse across a gas-permeable membrane on an electrode. Total urine nitrogen was determined using a nitrogen analyser (Antek, Houston, Texas, USA). Urinary and serum urea and creatinine levels were determined on a Technicon Autoanalyzer II (Technicon, Tarrytown, New York, USA).

Calculations

Cardiac output was calculated using the Fick method[13]. The cardiac index was determined by dividing the cardiac output by body surface area, which was calculated from body-weight.

For each amino acid under consideration, the individually determined limb flow rate was multiplied by the corresponding arteriovenous substrate concentration difference to give a value for substrate flux. At each time point, the six resulting determinations of substrate flux across a limb (three from each limb) were used to calculate the mean single-limb flux. Amino acid nitrogen exchange was then calculated using the millimolar sum of nitrogen groups in the amino acids measured. In a separate calculation, the mean single-limb blood flow at each time point was obtained from the six individual measurements of flow at that time (three from each limb).

Statistical analysis

Statistical analysis was carried out using a standard statistical package (StatView 512+; BrainPower, Calabasas, California, USA). Analysis of variance (ANOVA) techniques were used to analyse the responses to treatment (TNF infusion and enterectomy), with repeated measurements of the indices over time (repeated-measures ANOVA). Four previously determined comparisons were made: control *versus* control plus enterectomy, control *versus* TNF, control plus enterectomy *versus* TNF plus enterectomy, and TNF *versus* TNF plus enterectomy. For variables not subjected to repeated measurement, data were analysed by factorial ANOVA. *Post hoc* comparisons were performed using the Scheffé *F* test. $P < 0·05$ was considered significant.

For the hindlimb blood flow and flux data, analysis was performed using SAS software, version 6.03 for the personal computer (SAS Institute, Cary, North Carolina, USA). TNF-treated and control animals were first compared using repeated-measures ANOVA to examine changes in response over time and to determine the effects of TNF administration. If significant main effects were detected, linear contrasts were used to test within-group differences and Tukey's studentized range highly significant difference test was used for comparisons between groups.

The operative stress associated with groin dissection was compared with that of animals not having a groin dissection by testing all initial values between groups. This analysis did not indicate any difference between groups, and so data from both groups of animals were pooled.

Results

General responses and haemodynamic changes (Table 1)

The four groups of animals did not differ with respect to weight or total dose of anaesthetic required, and arterial pH remained stable throughout the study. Blood pressure was normal and stable over the 6-h infusion period in intact and control animals subjected to enterectomy. TNF caused the mean blood pressure

Table 1 *General responses and haemodynamic changes*

	Controls		TNF-treated animals		Enterectomized controls		Enterectomized dogs receiving TNF	
	$t = 0$	$t = 6$	$t = 0$	$t = 6$	$t = 0$	$t = 6$	$t = 0$	$t = 6$
Arterial blood pressure (mmHg)	152(5)	146(4)	154(6)	97(7)*	163(7)	159(9)	150(4)	83(9)†
Heart rate (beats per min)	129(9)	139(11)	125(7)	175(7)‡	185(10)	188(10)§	176(7)	190(10)
Temperature (°C)	37·5(0·3)	38·6(0·2)	38·1(0·2)	39·5(0·5)#	37·5(0·3)	39·7(0·1)	37·7(0·5)	39·7(0·8)
Cardiac index (l min^{-1} m^{-2})¶	4·8(0·4)	3·7(0·4)	5·2(0·3)	3·0(0·3)	3·6(0·1)	3·0(0·3)	3·2(0·4)	2·2(0·2)

Values are mean(s.e.m.). TNF, tumour necrosis factor. *$P = 0·0001$ (*versus* controls); †$P = 0·002$ (*versus* enterectomized controls); ‡$P = 0·007$ (*versus* controls); §$P = 0·01$ (*versus* controls); #$P = 0·01$ (*versus* controls) (repeated-measures analysis of variance); ¶statistical analysis not feasible because of small numbers to fall in both intact and enterectomized dogs. TNF administration and enterectomy both led to tachycardia; TNF also caused a significant rise in body temperature. In intact animals the cardiac indices were similar and fell with time in both groups. Hindlimb blood flow decreased in controls and TNF-treated animals (*Table 2*); it was significantly lower in the latter at 3 and 6 h ($P < 0.02$).

Substrate concentrations

In the control animals the mean(s.e.m.) arterial amino acid nitrogen concentration was 4·7(0·4) mmol l^{-1} initially and 4·7(0·3) mmol l^{-1} at 6 h (*Figure 1*). In animals receiving TNF the value at $t = 0$ was 4·8(0·1) mmol l^{-1} and 5·6(0·2) mmol l^{-1} at 6 h. After removal of the intestine the level for amino acid nitrogen in controls was 4·5(0·2) mmol l^{-1} at $t = 0$ and 5·1(0·5) mmol l^{-1} at 6 h. In those given TNF the value at $t = 0$ was 4·3(0·2) mmol l^{-1} and 4·6(0·4) mmol l^{-1} at 6 h.

The mean(s.e.m.) serum urea nitrogen concentration in intact controls was 15·6(1·3) mg dl^{-1} at $t = 0$ and 12·1(1·0) mg dl^{-1} at 6 h. In dogs given TNF the value was 17·4(0·6) mg dl^{-1} at $t = 0$ and 14·0(1·4) mg dl^{-1} at 6 h. In controls the mean(s.e.m.) serum creatinine level at $t = 0$ was 0·7(0·03) mg dl^{-1} and 0·6(0·04) mg dl^{-1} at 6 h. The creatinine concentration at the start of the study in dogs given TNF was 0·8(0·03) mg dl^{-1} and 0·9(0·07) mg dl^{-1} at 6 h. Enterectomized controls began with a mean(s.e.m.) urea level of 15·5(2·8) mg dl^{-1} and at 6 h had a level of 11·0(2·3) mg dl^{-1}. In TNF-treated animals the value was 14·3(0·5) mg dl^{-1} at $t = 0$ and 15·2(1·9) mg dl^{-1} at 6 h. The mean(s.e.m.) creatinine concentration in controls that had undergone enterectomy was 0·6(0·07) mg dl^{-1} at $t = 0$ and 0·6(0·06) mg dl^{-1} at 6 h. In enterectomized dogs receiving TNF the value was 0·7(0·03) mg dl^{-1} at $t = 0$ and 1·0(0·15) mg dl^{-1} at 6 h.

For these three substrates (making the four previously determined comparisons), there were no significant differences between groups at $t = 0$ or 6 h, except that intact TNF-treated dogs had significantly higher creatinine levels than intact control animals at 6 h ($P < 0.05$).

Table 2 *Hindlimb blood flow and weights*

Group	Time (h)	Limb blood flow (ml min^{-1})	Limb weight (g)	Limb muscle weight (g)
Controls ($n = 6$)	0	183(22)	1895(64)	1228(36)
	3	177(21)		
	6	153(19)		
Tumour necrosis factor ($n = 6$)	0	171(23)	2022(107)	1297(69)
	3	110(10)*		
	6	93(16)*		

Values are mean(s.e.m.). $*P < 0.02$ (*versus* controls at 3 and 6 h; analysis of variance)

Hindlimb flux (Figure 1)

At the start of the experiments, femoral arteriovenous concentration differences for amino acid nitrogen were similar and consistently negative in the two groups. Amino acid nitrogen flux was also similar in the two groups and did not change significantly during the infusion period.

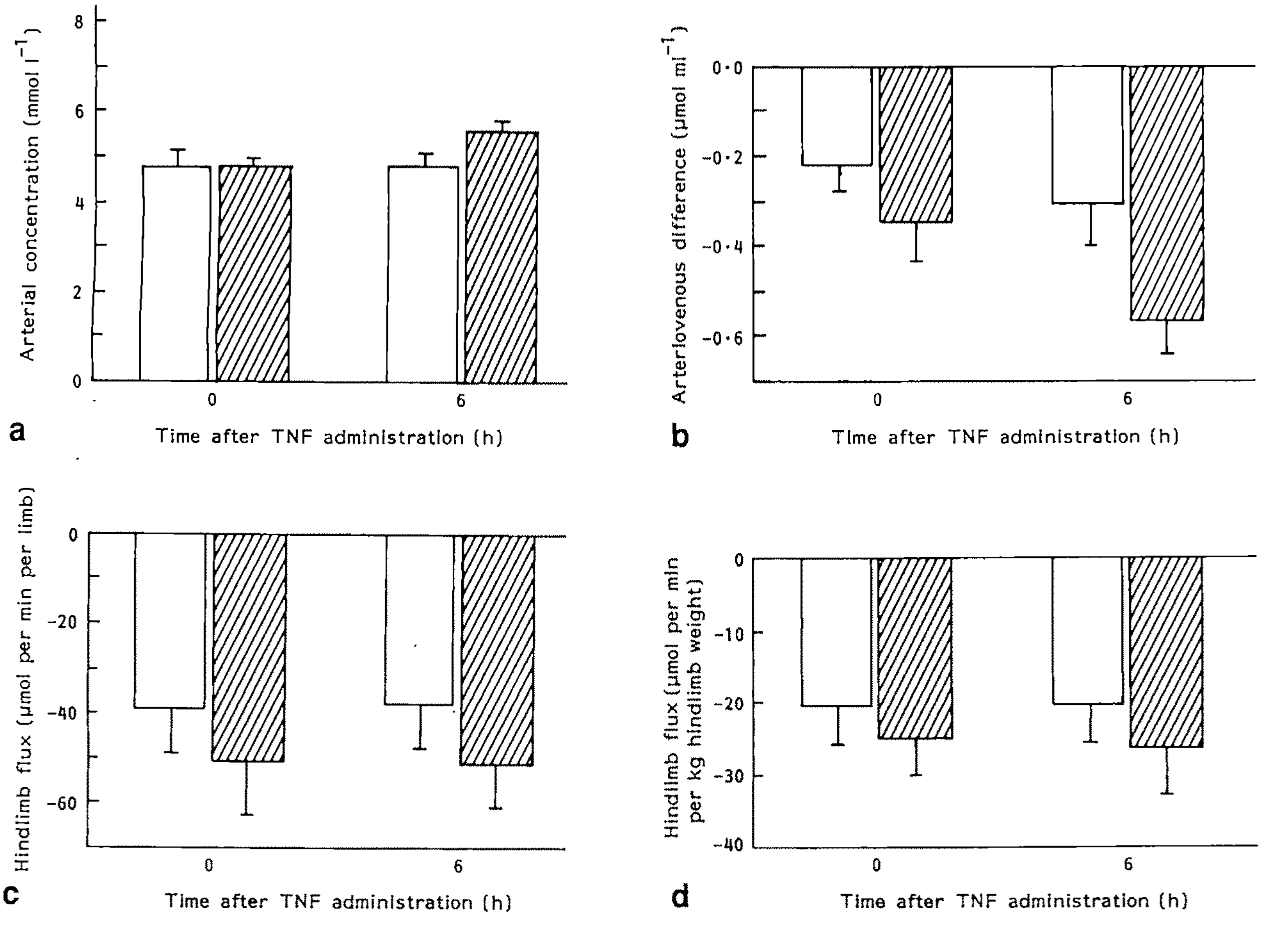

Figure 1 *Changes in amino acid nitrogen* **a** *arterial concentrations,* **b** *arteriovenous difference, and* **c** *and* **d** *hindlimb flux. Values are mean(s.e.m.). TNF, tumour necrosis factor.* □, *Controls* (n = 6); ■, *TNF-treated animals* (n = 6). *For all variables, there were no differences between the two groups at any of the time points*

Table 3 *Urinary parameters*

	Controls ($n = 12$)	TNF-treated animals ($n = 9$)	Enterectomized controls ($n = 4$)	Enterectomized dogs receiving TNF ($n = 6$)
Volume of urine (ml kg^{-1})	5·2(1·5)	22·4(3·0)*	2·7(0·4)	5·5(1·8)†
Total nitrogen (mg kg^{-1})	113(8)	165(15)*	101(7)	86(18)†
Urea nitrogen (mg kg^{-1})	96(9)	148(15)*	93(12)	79(17)†
Creatinine (mg kg^{-1})	6(3)	10(8)*	6(1)	6(1)†
Ammonia (mg kg^{-1})	4(1)	4(1)	3(0·5)	2(0·5)

Values are mean(s.e.m.) 6-h values corrected for body-weight. * $P < 0\cdot05$ (*versus* controls); † $P < 0\cdot05$ (*versus* intact TNF-treated animals) (factorial analysis of variance)

Urinary parameters (Table 3)

During the 6 h of study, the mean(s.e.m.) volume of urine passed by intact control dogs was 5·2(1·5) ml kg^{-1}; the urine volume for TNF-treated dogs, 22·4(3·0) ml kg^{-1}, was significantly greater ($P < 0\cdot05$). TNF-treated animals excreted a significantly greater amount of nitrogen than control dogs ($P < 0\cdot05$), which was accounted for by a significantly greater excretion of creatinine ($P < 0\cdot05$) and urea nitrogen ($P < 0\cdot05$). There were no differences in ammonia excretion.

The 6-h urine volume excreted by enterectomized controls was not significantly different from that of intact controls. The enterectomized dogs that received TNF had similar 6-h urine volumes to controls, but the values were significantly lower than those of intact dogs receiving TNF ($P < 0\cdot05$). Total urinary nitrogen, urea nitrogen and creatinine excreted in the two groups of animals subjected to enterectomy did not differ from each other, or from values found in intact controls. The total urinary nitrogen excreted by enterectomized dogs receiving TNF was significantly less than that excreted by intact dogs receiving TNF ($P < 0\cdot05$), as was the excretion of urinary urea ($P < 0\cdot05$) and creatinine ($P < 0\cdot05$).

Discussion

The purpose of this study was to examine the effects of TNF infusion on protein metabolism. A 6-h sublethal infusion of TNF led to a marked increase in urinary nitrogen excretion in anaesthetized dogs. This occurred in the absence of acidosis or profound hypotension, and is in agreement with the findings of Mealy *et al.*[14] that a 6-day TNF infusion in rats leads to increased nitrogen excretion and negative nitrogen balance.

The 6-h total nitrogen excretion for animals receiving TNF was significantly greater than the value for controls. This could not be explained by changes in serum urea nitrogen, creatinine or total amino acid nitrogen concentrations. The serum urea concentration fell slightly in both groups, whereas animals receiving TNF demonstrated a small increase in the serum creatinine level. It seems unlikely that nitrogen excretion would continue at this rate for a prolonged period; a large early response followed by a gradual decline is more likely. However, if, for the purposes of comparison with other data, a 24-h value is calculated, the total excretion in this study would be 660 mg kg^{-1}, considerably greater than the mean(s.e.m.) nitrogen loss following a moderately sized laparotomy (492(20) mg per kg per 24 h)[15], and similar to the 20-h loss of 561 mg kg^{-1} reported for dogs with *Escherichia coli* sepsis[16].

The data on hindlimb flux indicate that the additional nitrogen lost in the urine of intact dogs given TNF was not derived from peripheral tissues (primarily skeletal muscle). Hulton *et al.*[15] found that mean(s.e.m.) basal postabsorptive hindquarter amino acid nitrogen flux was $-0\cdot5(5\cdot3)$ µmol min^{-1} kg^{-1}. By contrast, mean(s.e.m.) 'hindquarter flux' at 6 h following an abdominal procedure of moderate severity rose to $-19\cdot1(4\cdot1)$ µmol min^{-1} kg^{-1}. 'Hindquarter' flux was determined using distal aortic and caval catheters and would be expected to give values slightly greater than that arrived at by addition of the two single hindlimb flux values found in the present study. If, for the purposes of comparison, the combined (left plus right) hindlimb flux values are related to body-weight, then the mean(s.e.m.) values for the present study are $-3\cdot3(0\cdot9)$ µmol min^{-1} kg^{-1} for controls at $t = 0$ and $-3\cdot3(0\cdot8)$ µmol min^{-1} kg^{-1} at $t = 6$ h. Controls therefore had an efflux of amino acid nitrogen, similar to that reported for basal postabsorptive animals. Infusion of TNF resulted in no change in amino acid nitrogen release. The hindlimb flux of amino acid nitrogen in experimental canine endotoxaemia has not been reported, but skeletal muscle taken from rats that have previously received endotoxin does show increased protein degradation[17], and an increased efflux of amino acid nitrogen might therefore have been expected. These data provide no evidence for TNF having a net proteolytic effect in peripheral tissues, although it should be remembered that hindlimb efflux was not measured at any time between 0 and 6 h. This finding is in agreement with *in vitro* observations that TNF has little effect on the rate of skeletal muscle protein breakdown[18].

The additional urinary nitrogen that appears after TNF administration cannot be explained by changes in the circulating pool of urea and creatinine; neither can it be explained by increased release of amino acid nitrogen from the periphery. It is likely, therefore, that the mobilized nitrogen was drawn from visceral sources, probably liver or intestine in this acute experiment. Mealy and Wilmore[19] have recently shown that chronic administration of TNF is associated with a net increase in hepatic cellularity and DNA content. The acute effects of TNF on these parameters are not known, but a net breakdown of liver protein seems unlikely.

The second part of the present study examined the effects of TNF administration after one of two possible visceral sources of nitrogen, the intestine, had been removed. Total urinary nitrogen excretion in control enterectomized animals was similar to that of the non-enterectomized controls. TNF administration to dogs subjected to enterectomy did not alter urinary nitrogen excretion. This is in contrast to the increased nitrogen excretion that occurred in non-enterectomized animals. Enterectomy results in decreased body-weight and a decreased nitrogen pool; a proportionate reduction in nitrogen excretion might reasonably be expected. However, these were constant factors in the enterectomized dogs and should not influence comparisons between control enterectomized dogs and enterectomized animals that received TNF.

If TNF normally causes an increase in urinary nitrogen that is prevented by enterectomy, this suggests that the intestine is the first and immediate source of this nitrogen. This hypothesis is supported by the findings of Mealy *et al.*[14] that a 6-day infusion of TNF to rats is associated with a fall in jejunal mucosa DNA, protein content and villus height compared with controls.

These findings have depended on studies in anaesthetized animals. It is possible that anaesthesia may have influenced the results, although this was a factor common to all studies and there were no differences between groups in the mean total anaesthetic dose required. Limited studies in two conscious dogs have suggested that the responses of conscious animals to this dose of TNF infusion are qualitatively similar to those of the anaesthetized dog[20]. It should also be noted that in the present study TNF was infused intravenously for 6 h at a constant rate. The situation in human sepsis is likely to be very different as TNF is released in short bursts and also may have local effects without necessarily appearing in the circulation[21].

In summary, TNF administration to intact animals causes a marked increase in urinary nitrogen excretion without altering peripheral amino acid nitrogen exchange. After removal of the intestine this nitrogen loss is abolished, suggesting that the intestine is the source of the mobilized nitrogen. If this TNF effect were shown to be an important element in the human response to sepsis it could, particularly if continued over a period of days, have significant effects on intestinal barrier function.

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Method for diagnosing rejection in small bowel transplantation

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Diagnosis of rejection in small bowel transplantation by the identification of a host-cell infiltrate is hampered by the physiological trafficking of host lymphocytes to the 'gut-associated lymphoid tissue' of the graft. This study compared physiological host-cell infiltration of small bowel grafts with that occurring in rejection and stable immunosuppression. Physiological host-cell infiltration, where the graft does not present an immune stimulus to the host, was assessed by transplanting bowel from DA to (DA × PVG) F_1 hybrid rats. The extent of host-cell infiltration was determined by immunohistochemical analysis. In the lamina propria, considerable infiltration by host cells was seen, although it was significantly less than that in rejection or stable immunosuppression. By contrast, host cells were seen in the intraepithelial compartment only in rejection. Host-cell infiltration in the absence of an allogeneic stimulus suggests that histological identification of host cells in the lamina propria is not necessarily indicative of rejection. However, the presence of host cells in the intraepithelial compartment is specific for rejection in small bowel transplantation.

Transplantation of the small intestine has been technically feasible since the pioneering work of Lillehei *et al.*[1] in the late 1950s. However, modern immunosuppressive regimens that have been successful in preventing rejection in other forms of organ transplantation are less effective in recipients of intestinal allografts[2,3]. This is due to the large amount of organized lymphoid tissue within the intestine, which creates the potential for the dual immunological problems of rejection and graft *versus* host disease.

Rejection results in destruction of the mucosal barrier and translocation of bacteria into the host. This is a major cause of morbidity and mortality in human allografts[4]. The capacity of the intestinal graft to recover after treatment of a rejection crisis is uncertain, and so the ability to diagnose rejection early and accurately is a priority.

One of the classical methods of studying rejection in organ transplantation is to look for host-cell infiltration of the graft. However, experimental studies in small bowel transplantation have shown that there is considerable host-cell infiltration in stable grafts maintained by immunosuppression[5]. Much of this migration may be physiological recirculation of cells into the 'gut-associated lymphoid tissue' of the graft[6] rather than infiltration provoked by an immunological stimulus.

Physiological cell migration can be assessed using a semiallogeneic small bowel transplant between inbred parental donors and F_1 hybrid recipients. Rejection does not occur in this model because all the major histocompatibility complex (MHC) antigens possessed by the graft are shared with the host. Therefore, any host-cell infiltration of graft tissues occurs in the absence of an allogeneic stimulus.

The aim of this study was to determine the degree of physiological host-cell infiltration that occurs in small bowel grafts, and to compare this with the infiltrate seen in fully allogeneic transplants.

Materials and methods

Surgery

Heterotopic vascularized accessory small bowel transplantation was carried out in rats using standard microvascular techniques[7]. The donor superior mesenteric artery was anastomosed to the recipient aorta and the donor portal vein to the inferior vena cava. The ends of the transplanted bowel were exteriorized as stomas in the form of a Thiry–Vella fistula.

Fully allogeneic transplants were performed between two inbred strains of rat (DA and PVG) that differed at the MHC. Semiallogeneic non-rejecting transplants were performed between DA strain donors and (DA × PVG) F_1 hybrid recipients.

Assessment of host-cell infiltration and graft survival

Small bowel grafts were harvested on days 1–8; the tissues were snap-frozen in liquid nitrogen and stored at −70°C.

Cryostat sections of harvested graft tissue were subjected to immunohistochemical analysis by an indirect immunoperoxidase technique. Two mutually exclusive monoclonal antibodies were used: OX27, which specifically recognizes PVG MHC class 1 antigens, and MN4, which recognizes DA MHC class 1 antigens[8]. After staining, the number of positive host cells was counted and expressed as a percentage of the total cell count seen in a high-power field. The areas selected for study were the lamina propria and intraepithelial compartment as

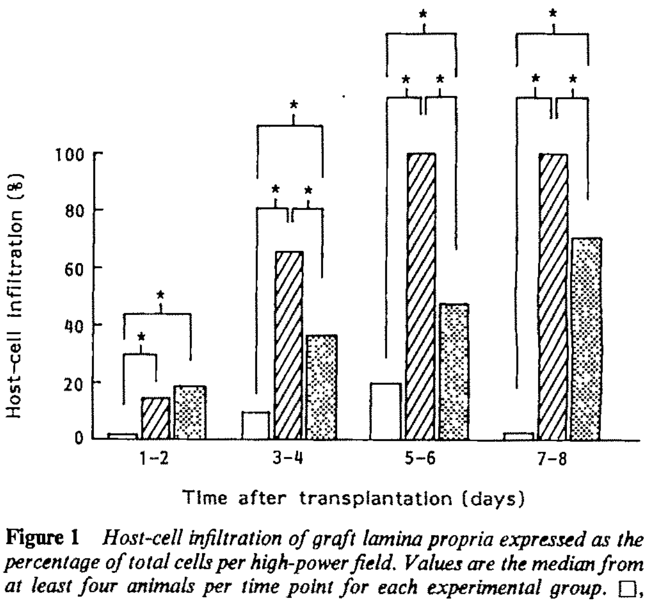

Figure 1 *Host-cell infiltration of graft lamina propria expressed as the percentage of total cells per high-power field. Values are the median from at least four animals per time point for each experimental group.* □, *Group 1;* ■, *group 2;* ▨, *group 3.* *$P < 0{\cdot}05$ (*Mann–Whitney* U *test*)

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these are tissues that would be obtained by endoscopic biopsy in the clinical setting.

Assessment of graft survival and acute rejection was made by haematoxylin and eosin staining of graft sections, looking for the accepted histological parameters of crypt hyperplasia, villus-tip oedema with blunting, and mucosal sloughing[9].

Experimental groups

Groups of rats underwent transplantation as follows: DA to (DA × PVG) F_1 hybrid – no immunosuppression (group 1); DA to PVG – no immunosuppression (group 2); DA to PVG with cyclosporin A immunosuppression (15 $\mathrm{mg\,kg^{-1}\,day^{-1}}$) administered by gavage from the day of transplantation (group 3).

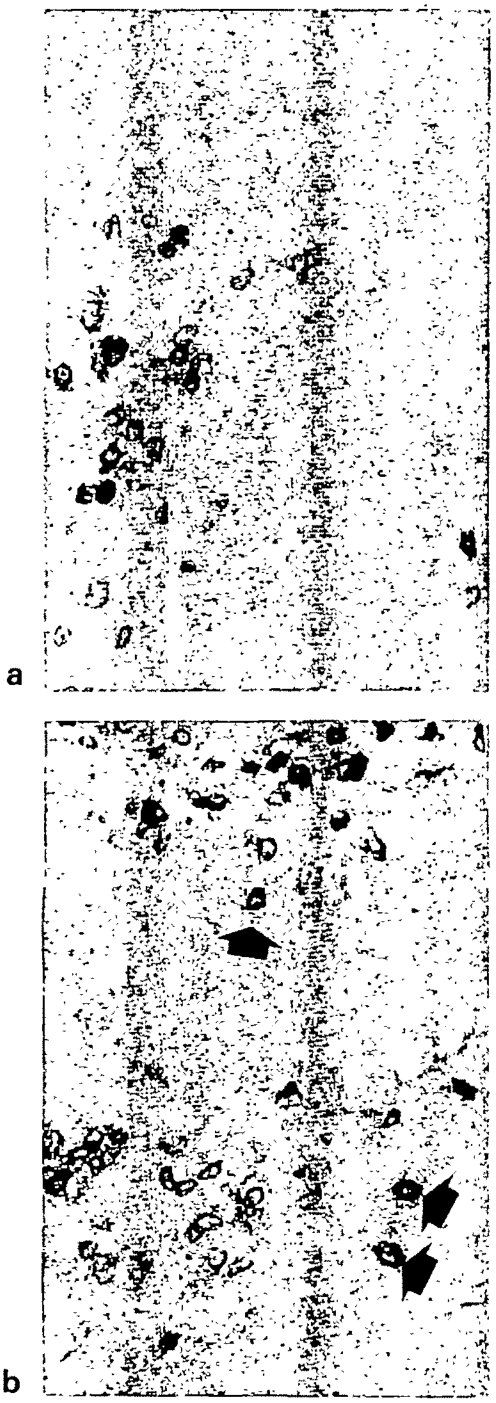

Figure 2 *Photomicrographs.* **a** *Villus from a non-rejecting small bowel graft 3 days after transplantation; no host cells can be seen in the intraepithelial compartment. (Indirect immunoperoxidase and haematoxylin stain, original magnification ×320).* **b** *Positively staining host cells (arrows) in the intraepithelial compartment on day 3 in the fully allogeneic transplant model before the development of overt rejection. (Indirect immunoperoxidase and haematoxylin stain, original magnification ×800)*

Results

Graft survival

In the fully allogeneic transplant group receiving no immunosuppression (group 2) there were histological signs of rejection shown by villus-tip oedema on day 5, leading to villus-tip sloughing on day 7, and eventually to mucosal sloughing by day 8. There was no histological evidence of rejection or ischaemia at any time in groups 1 and 3.

Host-cell infiltration

Lamina propria. There was a progressive increase in host-cell infiltration up to day 8 in rats receiving a fully allogeneic transplant (groups 2 and 3). In the semiallogeneic DA to (DA × PVG) F_1 combination (group 1), the number of infiltrating host cells increased steadily for 6 days after transplantation, but declined subsequently (*Figure 1*). At all times there was significantly greater host-cell infiltration of graft tissue in the fully allogeneic transplant groups (2 and 3) compared with the semiallogeneic combination. Comparing groups 2 and 3, there was a similar degree of infiltration at days 1–2 but after this there was a significantly greater infiltrate in the animals that proceeded to reject their grafts (group 2) compared with those stabilized by immunosuppression (group 3).

Intraepithelial compartment. In the fully allogeneic combination not receiving immunosuppression (group 2), host cells were detected in the intraepithelial compartment by days 3–4 (3 per cent); this rose to 5 per cent by days 5–6 after transplantation. After this, no assessment could be made because of graft epithelial damage from rejection. In the other two experimental groups, in which rejection did not occur, no host cells were seen in the intraepithelial compartment at any time in the study. The appearance of positively staining host cells in the intraepithelial compartment is illustrated in *Figure 2*.

Discussion

The major cause of morbidity and mortality following human small bowel transplantation is acute rejection[2,3], early diagnosis of which is dependent on analysis of endoscopic mucosal biopsies[10]. The histological changes suggestive of rejection include villus-tip oedema leading to villus-tip blunting and loss, crypt hyperplasia and, eventually, mucosal sloughing. However, ischaemic injury is not uncommon after any microvascular transplant procedure and may produce similar histological changes[9]. Histochemical staining of epithelial cells for cytoplasmic enzymes has been advocated as a diagnostic test for rejection but may also be affected by ischaemia, which reduces epithelial enzyme production[9].

Host-cell infiltration has been used to diagnose rejection in other forms of organ transplantation. This study assessed the value of the technique in small bowel transplantation by determining physiological infiltration[6] of the graft by host cells in the absence of rejection. In experimental group 1, small bowel from an inbred parental donor (DA) was transplanted to a (DA × PVG) F_1 hybrid recipient. As all the MHC antigens possessed by the graft were shared with the recipient, there was no allogeneic stimulus to host-cell infiltration. No tissue sections showed any histological evidence of ischaemic damage and the host-cell infiltrate seen was thus confirmed to be physiological rather than immunological. From day 6 onwards there was a fall in the number of infiltrating host cells in this group. It is possible that, in the graft tissue, the host cells (DA × PVG) present an antigenic challenge to the native graft cells (DA). The latter therefore mount an *in situ* graft *versus* host response towards the infiltrate. The pattern of positive host-cell staining seen from day 6 onwards was less discrete than before. This is consistent with the cellular antigen shedding that occurs when a cell undergoes immune attack, and supports the hypothesis of a local graft *versus* host reaction.

Statistical analysis showed the physiological infiltration of the lamina propria in group 1 to be significantly less than the immunologically induced migration seen in groups 2 and 3. The extent of this difference was similar at 1–2 days after transplantation. After this, rats proceeding to rejection had a greater degree of infiltration than those with stable grafts maintained by immunosuppression. These data indicate that host cells migrate physiologically to the lamina propria, and therefore their presence is not necessarily indicative of rejection. In contrast to the lamina propria, there was no physiological infiltration of host cells into the intraepithelial compartment. Host-cell infiltration of this compartment occurred only in the rejection group. The presence of this infiltrate from day 3 preceded histological evidence of rejection, which occurred from day 5 after transplantation. The absence of host cells in the intraepithelial compartment of the semiallogeneic group and in animals maintained on immunosuppressive therapy shows this to be a specific site for diagnosing rejection in small bowel transplantation.

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Announcement

Eurosurgery 93 – 14–17 September 1993

Poster Competition for Surgical Trainees

The organizing committee of Eurosurgery 93 wishes to announce a poster competition, with a prize of 700 ecus (approximately £500) and a commemorative medallion. This competition is open to trainees in any surgical specialty for a poster presented at Eurosurgery 93.

Abstracts are invited from all trainees; those who have already had a poster accepted at the meeting will automatically be eligible for the prize. Trainees who wish to present a poster for this prize should write for further details and registration forms to Rebecca Baldry, Eurosurgery Organizing Committee Secretary, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK. Fascimile: 071 831 9438.

Abstracts, of not more than 200 words and clearly labelled 'Trainees' Poster Competition', should be sent to Rebecca Baldry at the Department of External Affairs at the College by 25 August 1993.

Registration at the meeting for trainees will be at the reduced rate of £90 per day or £250 for the full 3 days of the meeting.

Accommodation is available to trainees at the modest cost of £60 for 3 nights' bed and breakfast.

J. P. S. Lumley

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Surgical polypectomy of duodenal adenomas in familial adenomatous polyposis: experience of two European centres

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Between 1978 and 1988, 12 patients with familial adenomatous polyposis (FAP) and severe duodenal polyposis underwent duodenotomy and duodenal polypectomy. The patients were from two separate institutions; all were women, with a mean age of 45·6 (range 25–62) years at the time of duodenotomy. Recurrent duodenal polyposis was detected at endoscopy in all 12 patients, at a mean of 13·3 (range 5–36) months after duodenotomy. All patients had moderate to severe duodenal polyposis at the time of the last endoscopic examination. Local excision of duodenal adenomas is an unsatisfactory treatment option in those with FAP. The ideal management of patients with FAP who have severe duodenal polyposis remains uncertain.

Familial adenomatous polyposis (FAP) is characterized by numerous adenomatous polyps throughout the intestinal tract. In the large bowel one or more of these polyps will undergo malignant change, but prophylactic colectomy all but eliminates the risk of colorectal cancer. In the foregut, there is an excess risk of cancer in the duodenum[1,2]. Although the risk for duodenal cancer does not approach that for large bowel carcinoma, duodenal cancer accounts for the majority of cancer-related deaths after colectomy. For example, of 222 patients with FAP who underwent colectomy and ileorectal anastomosis at St Mark's Hospital, London, between 1948 and 1990, 11 have died as a result of duodenal cancer while five have died from rectal cancer.

Almost all patients with FAP have duodenal adenomas, but these are not usually amenable to conventional endoscopic or surgical treatment[3]. This is because there may be many adenomas, they are most commonly sessile, and they frequently cluster around the ampulla of Vater. Diathermy or surgery around the ampulla carries the risk of scarring and narrowing of the ampullary orifice. Moreover, only in some patients do duodenal adenomas progress along the adenoma–carcinoma sequence, becoming larger, more villous and more dysplastic[4]. As they do so, prophylactic measures to prevent malignant change may become necessary. One option available is duodenotomy and local excision of duodenal polyps. The aim of this study was to determine the outcome of patients in whom this approach had been used.

Patients and methods

Patients with FAP who had undergone duodenotomy and excision of adenomas were identified from the records of the St Mark's Polyposis Registry, London, and from the medical records of the Hôpital St Antoine, Paris. Data obtained from retrospective review of these records included the type of colorectal resection performed, the patient's age and the findings at each upper gastrointestinal endoscopy session (including histology), surgical technique, histopathology of the excised duodenal adenomas, date of endoscopy at which any recurrence of duodenal adenomas was noted, and the subsequent course of each patient. Surgery for duodenal polyposis consisted of duodenotomy in the second part of the duodenum. All adenomas >1 cm in diameter had been removed by local excision and the remaining duodenum cleared of polyps by either excision or diathermy in all but one patient.

The severity of duodenal polyposis was classified according to a system previously described[3] in which stage I represents mild disease and stage IV severe duodenal polyposis. Variables that worsen the stage of duodenal polyposis in this system are increasing number, size, villous morphology and degree of dysplasia of adenomatous polyps.

Results

Duodenotomy and clearance of duodenal adenomatous polyps had been performed in 12 patients from 11 families between 1978 and 1988. Of these, seven patients were from London and five from Paris. All patients were women, with a mean age of 45·6 (range 25–62) years and all had stage IV duodenal polyposis at the time of duodenotomy. Colectomy and ileorectal anastomosis had been performed in six patients, restorative proctocolectomy with ileoanal anastomosis in four and proctocolectomy with ileostomy in two.

The findings at duodenotomy and the histopathology of the most advanced duodenal adenomas excised from each patient

Table 1 *Findings at duodenotomy*

	Duodenal lesions			
Patient no.	No.	Size of largest (cm)	Histological findings	No. of polyps excised
St Mark's Hospital				
1	>20	4	Villous; severe dysplasia	2
2	>20	3	Tubulovillous; moderate dysplasia	1
3	10–20	1·5	Tubulovillous; moderate dysplasia	4
4	10–20	1·5	Tubulovillous; moderate dysplasia	5
5	>20	2	Tubular; moderate dysplasia	3
6	>20	1·5	Tubulovillous; moderate dysplasia	9
7	10–20	3	Tubulovillous; moderate dysplasia	2
Hôpital St Antoine				
8	>20	1·5	Tubulovillous; moderate dysplasia	1
9	5–10	2·5	Villous; severe dysplasia	1
10	5–10	2	Villous; severe dysplasia	5
11	10–20	3	Villous; moderate dysplasia	2
12	10–20	2	Villous; moderate dysplasia	1

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Table 2 *Follow-up data*

	First endoscopy		Endoscopy before duodenotomy		First endoscopy after duodenotomy		Last endoscopy	
Patient no.	Age (years)	Stage#	Age (years)	Stage#	Time after duodenotomy (months)	Stage#	Time after duodenotomy (months)	Stage#
St Mark's Hospital								
1	55	IV	55	IV	7	I	36	IV
2*	56	II	61	IV	12	II	48	II
3†	34	IV	34	IV	7	II	132	IV
4†	44	II	51	IV	5	III	24	IV
5	49	III	49	IV	9	II	150	IV
6	51	III	57	IV	6	II	84	IV
7‡	34	Insufficient data	38	IV	36	III	36	III
Hôpital St Antoine								
8*	24	IV	25	IV	6	II	36	IV
9§	43	IV	43	IV	12	III	12 36	IV III
10*	43	IV	43	IV	12	I	72	II
11*	29	IV	29	IV	12	II	72	III
12	62	IV	62	IV	12	0	36	II

*Receiving therapy that may alter the natural history of duodenal polyposis. †Died from jejunal carcinoma (no. 4) and carcinoma of unknown primary (no. 3). ‡Patient did not have total clearance of the duodenum at duodenotomy. §Repeat duodenotomy performed 12 months after the first; 36 months is the time from the first duodenotomy. #Stage of duodenal polyposis: I, mild to IV, severe

are shown in *Table 1*. Excision at duodenotomy yielded 36 adenomatous polyps; in no case was the polyp histology at duodenotomy more severe than that found at endoscopic biopsy. Duodenal polyposis recurred in all 12 patients (*Table 2*). Endoscopy was performed at variable times after operation. Recurrence was documented at endoscopy at a mean time from duodenotomy of 13·3 (range 5–36) months. The mean time to documentation of recurrence was 11·7 months for the St Mark's patients and 15·6 months for those from Hôpital St Antoine. Stage IV duodenal polyposis redeveloped in seven patients, while three were found to have stage III duodenal disease and two stage II disease at the latest endoscopy. Four patients (St Antoine, three; St Mark's, one) received treatment in addition to duodenotomy that may have altered the natural history of duodenal polyposis: two patients have been taking sulindac for desmoid disease, treatment starting 6 months after duodenotomy, and two underwent endoscopic removal of duodenal polyps. Of these four patients, only one has progressed to stage IV disease, while two have stage III and one stage II duodenal polyposis.

One other patient with recurrent stage IV disease (with severe dysplasia of a villous adenoma) underwent repeat duodenotomy 12 months after the first operation. Stage II duodenal polyposis was found at repeat endoscopy 12 months after the second operation.

Two patients have died from cancer, of the jejunum in one and from an unknown primary in the other.

Discussion

This study shows that duodenotomy and clearance of the duodenum fails to guarantee a polyp-free small bowel in patients with FAP. This is not surprising in view of current knowledge about the occurrence of microscopic adenomas in the duodenum[3] and the periampullary location of adenomas in many patients with FAP (where treatment may be difficult).

Approximately 10 per cent of patients with FAP at St Mark's Hospital develop stage IV duodenal polyposis[3]; the inability of local surgery to treat this problem satisfactorily highlights the difficulties in management that patients with severe duodenal polyposis represent. Pancreatoduodenectomy is one solution, but it has considerable potential morbidity and mortality which must be taken in account when dealing with premalignant disease.

Furthermore, in patients with FAP bile may promote tumour growth. This is suggested by the distribution of gastroduodenal adenomas[3] and the presence of severe gastroduodenal bile reflux in patients with FAP who have gastric adenomas[5]. The bile of patients with FAP may contain carcinogens, which might contribute to the characteristic damage to DNA (adduct formation) that has been detected in the mucosa of these patients[6] and in healthy target mucosa exposed to bile from patients with FAP[7]. Pancreatoduodenectomy necessitates displacement of the bile duct to another area of the small bowel; this would allow possibly genotoxic bile to exert its effects at a new site, with a theoretical risk of new adenoma growth. The therapy of advanced duodenal polyposis remains unsatisfactory. It is recommended that all patients, including those who have undergone duodenotomy, should have regular endoscopic surveillance. Intervention should be reserved for those in whom polyps are seen to grow rapidly, or where induration or severe dysplasia is found. If malignancy occurs, pancreatoduodenectomy is indicated.

The ideal treatment will have a low morbidity rate and a high therapeutic effect. Photodynamic laser therapy and administration of non-steroidal analgesics are two such potential treatments currently under study at St Mark's Hospital.

Acknowledgements

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Short note

Br. J. Surg. 1993, Vol. 80, August, 1029

Mesenteric infarction: improved survival rate after temporary enterostomy

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The overall survival rate of patients with acute intestinal ischaemia has changed little despite improvements in vascular surgical technique and intensive care. The most important reason is the persistence or recurrence of small bowel ischaemia[1–3]. Since 1975, the policy of the authors has been to perform enterostomy and create a mucus fistula without anastomosis when doubt exists about small bowel viability and when peritonitis is present. This policy is applied to patients with intestinal ischaemia and gut necrosis.

Patients and methods

Between 1980 and 1990, 29 patients underwent small bowel resection and temporary enterostomy with creation of a mucus fistula for mesenteric infarction. These interventions represented 85 per cent of operations for intestinal ischaemia in the same period. The remaining patients underwent resection and primary anastomosis for very short ischaemic lesions without peritonitis. There were 18 men and 11 women with a mean age of 63 (range 27–86) years.

Infarction involved a segment of jejunum or ileum in 11 patients and the whole of the small bowel in a further 11; the seven remaining patients had associated colonic infarction. The aetiology was arterial occlusion in 18 cases, venous occlusion in eight and non-occlusive ischaemia in three. Eight patients had acute peritonitis.

Of 29 intestinal resections performed, six were extended to the right and three to the left colon. In all cases, enterostomy was performed and a mucus fistula created. In four patients, separate resections were necessary for discontinuous lesions; in these patients the bowel ends were exteriorized as a proximal ileostomy and three distal mucus fistulas. Survival and postoperative complications were reviewed.

Results

Ten of the 29 patients died. Three succumbed during the early postoperative period from progressive overwhelming septic shock and four died following cardiopulmonary complications during the first month after operation. Relaparotomy was performed in nine patients. Two patients underwent a planned second-look procedure, one of which revealed progressive venous mesenteric infarction. Two further patients showed recurrence of ischaemia. Two patients developed an intra-abdominal abscess and one had an intra-abdominal haematoma that required surgical drainage. One patient suffered abdominal wound dehiscence. Three of the patients who underwent relaparotomy died. Thirteen patients survived after a single procedure with favourable outcome. All survivors (19 patients) had bowel continuity re-established between 6 and 12 weeks after the initial procedure, with no mortality or morbidity.

Discussion

The low incidence of small bowel ischaemia, its various causes and the variety of associated medical disorders make it difficult to perform a randomized trial for this condition. The overall survival rate in the present series of 66 per cent compares favourably with those of other studies[1,2,4]. Primary anastomosis is associated with a high mortality rate owing to progressive ischaemia and anastomotic leakage[5]. The risk of anastomotic leakage was avoided in the present study by adopting a policy of exteriorization of the bowel ends with reanastomosis following recovery from the initial episode. Only one-third of the present patients required relaparotomy. The bowel ends are readily observed and evidence of progressive ischaemia can be detected. The need for planned second-look procedures was avoided, except in venous intestinal ischaemia where injury may be discontinuous and less easily predicted. Pathophysiological studies have shown that distension, intraluminal stasis and bacterial overgrowth may compound the risk of recurrent ischaemia. These factors are minimized by avoiding primary anastomosis, and probably account for the low recurrence rate of 10 per cent.

A policy of bowel resection with delayed reanastomosis is recommended in patients with acute intestinal ischaemia. This procedure confers no additional mortality or morbidity.

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Surgical workshop

Br. J. Surg. 1993, Vol. 80, August, 1030

Incisional hernioplasty with a 'flower' polypropylene prosthesis

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Abdominal incisional hernia with a myoaponeurotic defect <10 cm wide is usually treated by simple suture or by some modified procedure such as those suggested by Judd or Welti and Endel[1]; 15–20 per cent of such cases are not treated successfully using these approaches. Unfortunately, the relevant literature often does not mention the duration of follow-up or give other important data[2,3]. The results are, nevertheless, poor enough to justify a different approach to the problem, as pointed out by Stoppa *et al.*[4].

Surgical technique

The 'flower' is a prosthesis made from polypropylene mesh. A polypropylene purse-string suture is passed around a circle (2–3 cm diameter) in the centre of a polypropylene mesh disc. The suture is then tied so that the synthetic material takes on a flower-like appearance (*Figure 1*). While the prosthesis is shrunk it can be passed through the hernia defect and the edges resected after the mesh has been positioned correctly.

Insertion of the prosthesis is rapid and simple under general anaesthesia. The skin and hernia sac are managed conventionally; the old scar is excised and the sac is opened, its contents removed, and the excess material resected. However, intra-abdominal adhesions are not dissected. The prosthesis is folded and inserted deep into the limited intraperitoneal space which, after its expansion, is completely filled with prosthetic mesh. The peritoneomyoaponeurotic defect may then be closed with a single row of interrupted sutures. If no adhesions are found, the prosthesis is inserted into the preperitoneal space. The 'flower' should overlap the edges of the defect by at least 2 cm. Drains are unnecessary.

Results

Thirty-one patients with minor incisional hernia have undergone surgery since January 1989. Eighteen had at least one of the following characteristics: obesity, diabetes, history of taking steroids and cirrhosis. There were no deaths and no major complication.

Patients were examined at 10, 30 and 90 days after operation and then every 6 months for 2 years. Thereafter, examination was once a year. The mean follow-up to date is 11 months. Although some patients who live far from the hospital have communicated by writing or by telephone, none has been lost to follow-up. At present there has been no hernia recurrence.

All patients had antibiotic prophylaxis parenterally during operation, followed by oral antibiotic for 5 days. None rejected the prosthesis or suffered a local infection. Two wounds became superficially inflamed, but the problem resolved rapidly. There was no seroma or haematoma. All patients returned home on the first or second day after operation.

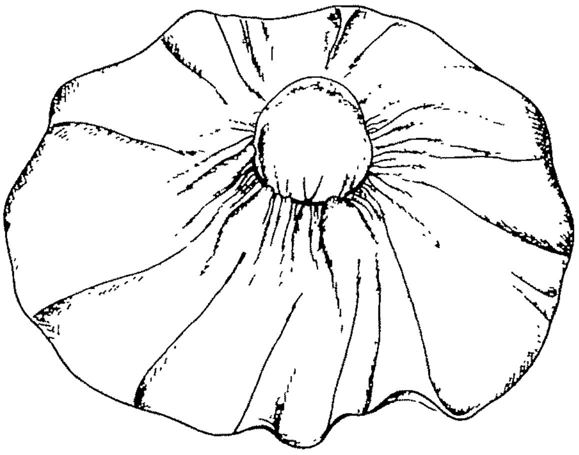

Figure 1 *The suture is left loose and then tied, allowing the synthetic material to achieve a flower-like appearance*

Discussion

The results of treating minor incisional hernia by conventional methods are good but not excellent. Stoppa and colleagues[4] suggested the use of a Mersilene (Ethicon, Norderstedt, Germany) prosthesis. Polypropylene mesh has been used for 30 years and is completely tolerated because it becomes fully incorporated in the tissues[5]. Infection is rare. Also, polypropylene mesh is not excessively soft, making it easy to handle and insert.

The repair of minor incisional hernia with a prosthesis may be justified if the procedure is simple, effective and safe. Increasing importance is attached to shortening the postoperative hospital stay to reduce costs. Repair of minor incisional hernia early may prevent it from becoming large and the polypropylene flower-shaped prosthesis seems to have advantages in all of the above respects.

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Duodenal duplication causing segmental portal hypertension and massive intestinal haemorrhage

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Duplication of the duodenum usually presents with intestinal obstruction in childhood but may undergo ulceration and bleeding. The gastro-oesophageal group of portasystemic collaterals is the most common site for bleeding in portal hypertension, but varices have occasionally been described elsewhere in the gastrointestinal tract. These 'ectopic' varices may be caused by generalized portal hypertension, when they can accompany oesophageal varices[1], or by isolated superior mesenteric vein (SMV) obstruction with a normal blood flow pattern in the portal and splenic veins[2].

A patient is presented who had massive intestinal bleeding associated with segmental portal hypertension caused by obstruction of the SMV by a duodenal duplication.

Case report

A 48-year-old woman presented with a few days' history of melaena. The haemoglobin level was 3·8 g/dl; liver function was normal. Endoscopy demonstrated no bleeding point in the stomach or duodenum. Barium enema suggested the possibility of right-sided colitis, but this was not confirmed by colonoscopy. Superior mesenteric angiograms showed a normal arterial pattern with no evidence of active bleeding. The venous phase demonstrated no flow in the SMV. The vessel was replaced by varices that did not appear to communicate directly with the portal vein. The splenic and portal veins were patent (*Figure 1*). The bleeding was therefore assumed to be caused by segmental portal hypertension resulting from SMV obstruction of unknown aetiology.

The patient continued to bleed and laparotomy was carried out. The small bowel distal to the duodenojejunal flexure was found to be filled with fresh blood. In the area normally drained by the SMV there were numerous varicose-type veins coursing towards the root of the small bowel mesentery. There was no evidence of liver cirrhosis, the spleen was not enlarged and the portal vein was patent. The main trunk of the SMV was encircled by a tubular duplication of the third part of the duodenum, and the vessel appeared to be thrombosed. The duplication was excised and the portal circulation was decompressed with a mesocaval shunt, using an end-to-side anastomosis between the right ovarian vein and one of the large collaterals.

The postoperative course was uneventful with no further bleeding. The patient remains well 12 months later.

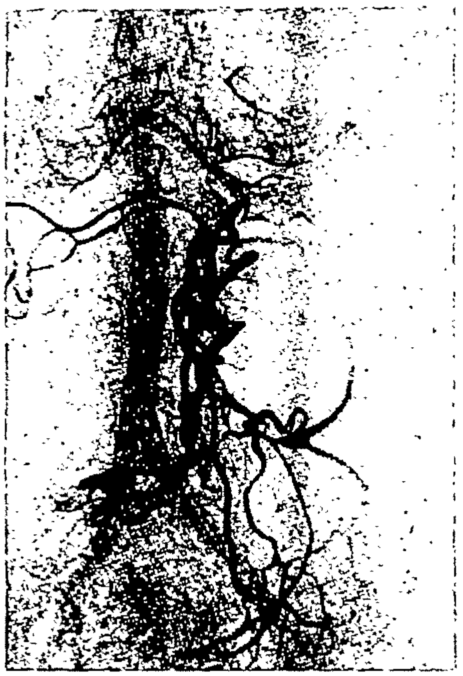

Figure 1 *Venous phase of a superior mesenteric angiogram showing occlusion of the superior mesenteric vein and the collateral varices*

Discussion

Duodenal duplication is a rare malformation of the alimentary tract, most commonly diagnosed during infancy and early childhood as a cause of intestinal obstruction. Morphologically, duplications are either spherical or tubular cystic lesions, usually located in the first or second part of the duodenum and often communicating with the lumen.

In adults the presenting symptoms are non-specific and the diagnosis is most commonly established during the treatment of complications related to the anatomical anomaly. An association between duodenal duplication and relapsing pancreatitis, most probably through intermittent compression of the pancreatic duct, has been well documented[3]. Malignant transformation and massive haemorrhage from an ulcer in the duplication mucosa have also been reported[4,5].

The present report is believed to be the first of segmental portal hypertension caused by obstruction of the SMV by duodenal duplication. A previous case of isolated duodenojejunal varices and SMV occlusion was not attributed to any anatomical abnormality, and the mechanism of venous obstruction was not established[2].

In the absence of other common pathological findings, segmental portal hypertension, although rare, should be included in the differential diagnosis of intestinal haemorrhage. Unless it can be demonstrated by selective splanchnic angiography, the exact cause of venous obstruction will probably remain unclear until the time of surgical exploration.

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Pattern of recurrence after hepatic resection for colorectal metastases

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Between 1978 and 1989, 159 patients with liver metastases from colorectal cancer underwent hepatic resection. Of 134 patients in whom metastases were confined to the liver, 109 had tumours removed completely with histologically negative resection margins. Two patients died in hospital. Ultrasonographically guided partial resection was performed in 80 patients, lateral segmentectomy in seven and lobectomy in 22. The 5-year survival rate of patients undergoing potentially curative resection was 47·9 per cent. Patients with metachronous tumours showed a significantly better prognosis than those with synchronous lesions in both univariate ($P < 0·01$) and multivariate ($P = 0·01$) analysis. During a median follow-up of 35·4 months, 64 patients developed recurrence, including 34 in the liver, 20 in the lung and 12 in the abdominal cavity. Of those with hepatic recurrence, ten patients developed tumours at the initial resection bed, seven in the same lobe, five in the contralateral lobe and 12 in both lobes. Ultrasonographically guided partial liver resection did not increase the risk of hepatic recurrence.

Liver metastases from colorectal cancer are common. Simultaneous hepatic metastases were observed in 11·8 per cent of 645 patients with colorectal cancer between 1985 and 1989, and 8·2 per cent of patients who underwent potentially curative surgery for primary lesions later developed liver secondaries. A similar figure was reported in a large series from Erlangen in Germany[1]. Advances in the treatment of these secondaries might contribute to an improved prognosis for such patients.

Carcinoembryonic antigen (CEA) assay, ultrasonography and computed tomography (CT) may allow an increased number of liver metastases to be detected at an early stage. A better understanding of hepatic anatomy[2–4], intraoperative ultrasonography[5] and recent developments in perioperative management have made liver surgery safer. Several reports[6–17] on hepatic resection have included patients who were treated before these new technologies were in clinical use.

This study evaluated the factors affecting survival and the pattern of recurrence after potentially curative hepatic resection in the past 12 years.

Patients and methods

Between January 1978 and December 1989, 159 patients with liver metastases from colorectal cancer underwent hepatic resection when (1) preoperative examination revealed that all liver tumours could be technically removed with conservation of adequate normal parenchyma and (2) there was no extrahepatic metastatic disease. Hepatic resection was considered in those with synchronous extrahepatic metastases if the extrahepatic tumours were resectable.

Ultrasonographically guided partial resection[18] (with a surgical margin >1 cm) was used to detect deposits not seen before operation[19,20], to confirm relationships between tumours and the intrahepatic vascular system[5,21] and to retain an adequate surgical margin. Lobectomy and left lateral segmentectomy was performed when considered technically easier.

Patients with colorectal cancer underwent ultrasonography to detect liver metastases before surgery and were followed with CEA assay and ultrasonography every 3 months, and chest radiography every 6 months. Abdominal CT was performed when hepatic recurrence was suspected from a raised CEA level or ultrasonography. Pulmonary CT was undertaken when chest radiography revealed possible lesions. In patients with a history of rectal cancer, pelvic CT was performed to exclude pelvic recurrence before hepatic surgery. After hepatic resection patients were followed using the same schedule.

The survival rate was estimated by the Kaplan–Meier method. The survival curve and recurrence rate were evaluated by the generalized Wilcoxon test and χ^2 analysis respectively. Cox's proportional hazards model was used in multivariate analysis to determine the significance of each variable, with survival as the endpoint.

Results

Of the 159 patients, six underwent non-curative surgery for primary lesions and 19 cases were complicated by simultaneous extrahepatic metastases. In the remaining 134 patients, metastases were confined to the liver. Eight patients had incomplete removal of hepatic tumour, so that 126 were considered to be clinically tumour-free. However, histological examination revealed positive resection margins in 17 patients. Therefore, 109 patients (81·3 per cent) underwent potentially curative hepatic resection.

The median follow-up was 35·4 (range 6–164) months and all surviving patients except one were followed for >2 years.

To analyse complications related to liver resection, 49 patients undergoing hepatic surgery alone (44 with metachronous, five with synchronous tumours) were studied. There were two deaths in the postoperative period after right lobectomy. Two patients had postoperative haemorrhage and intra-abdominal abscess, and minor complications (pleural effusion, wound abscess, bowel obstruction) were observed in nine.

The 3- and 5-year survival rates of patients undergoing potentially curative resection were 57·2 and 47·9 per cent respectively (*Figure 1*). Of 19 patients with extrahepatic disease, nine of 11 with intra-abdominal recurrence and five of nine with pulmonary metastases underwent simultaneous extrahepatic surgery; only two patients in this group survived. (One patient had both abdominal and pulmonary metastases.) Of the 17 patients with positive resection margins, none survived >3 years.

The 107 survivors undergoing curative resection consisted of 62 men and 45 women with a mean age of 57·7 (range 34–82) years. Patient details are summarized in *Tables 1* and *2*. Partial resection was performed in 74·8 per cent; five patients undergoing lobectomy combined with partial resection of the contralateral lobe were included in the lobectomy group.

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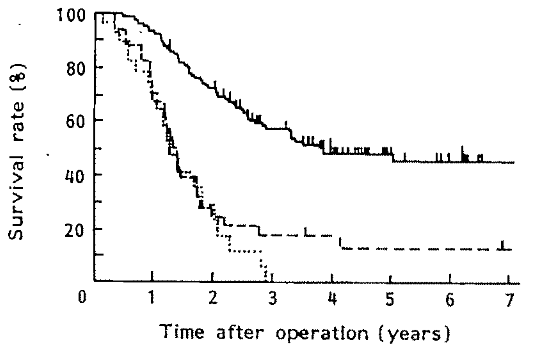
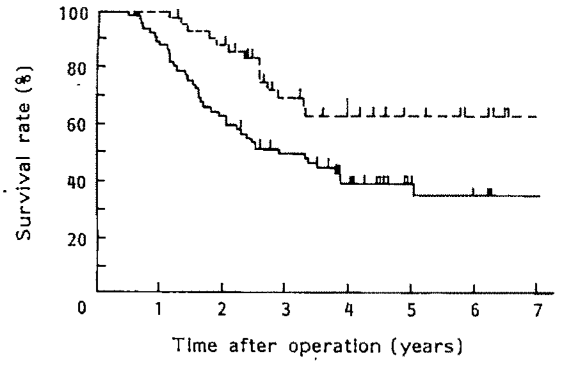


No. at risk

Curative	107	99	76	52	36	23	17	11
Positive margins	17	12	4	-	-	-	-	-
Extrahepatic	19	13	5	2	1	1	1	1

Figure 1 *Survival curves of patients undergoing potentially curative hepatic resection (——; n = 107), of those with positive resection margins (······; n = 17) and of those with extrahepatic metastases (– – –; n = 19). ⊥, Patients alive at last follow-up*



No. at risk

Synchronous	65	57	40	29	19	10	7	5
Metachronous	42	42	36	23	17	13	10	6

Figure 2 *Survival curves of patients with synchronous (——; n = 65) and metachronous (– – –; n = 42) metastases. ⊥, Patients alive at last follow-up*

Table 1 *Characteristics of primary tumours in 107 patients undergoing potentially curative hepatic resection*

	No. of patients
Location	
Right colon	17
Left colon	41
Rectum	49
Pathological grade	
Well differentiated	50
Moderately differentiated	48
Mucinous	5
Unknown	4
Nodal metastases	
Negative	32
Positive	69
Unknown	6

Table 2 *Details of liver tumours and hepatic recurrence rate in 107 patients undergoing potentially curative hepatic resection*

	No. of patients	Recurrence rate in liver remnant (%)
Time of diagnosis		
Synchronous	65	32·3
Metachronous	42	30·9
Location of tumour		
Right lobe	38	26·3
Left lobe	29	24·1
Bilobar	40	42·5
No. of metastases		
1	51	25·5
2–4	39	35·9
≥5	17	41·2
Tumour size (cm)		
≤2·0	39	33·3
2·1–5·0	35	27·9
≥5·1	33	36·0
Carcinoembryonic antigen level (ng/ml)		
≤5·0	22	27·2
5·1–30·0	33	42·4
≥30·1	51	27·5
Unknown	1	
Type of resection		
Partial	80	31·3
Lateral segmentectomy	7	42·9
Lobectomy	20	30·0

Patients with metachronous tumours showed significantly better prognosis than those with synchronous lesions in both univariate ($P < 0·01$) and multivariate (relative risk 2·57 (95 per cent confidence interval 1·23–5·37), $P = 0·01$) analysis (*Figure 2*). None of the other eight factors studied (location, histological grade and regional lymph node metastases of the primary tumour; location, number and size of liver tumours; preoperative CEA level; type of hepatic surgery) affected the prognosis.

Recurrence after curative resection was confirmed in 64 patients: in the liver in 34, in the lung in 20, in the abdominal cavity in 12 and in other organs in six (six showed recurrence in multiple organs). Thirty-three patients survived >3 years without relapse. Of those with synchronous tumours, 42 patients developed recurrence: 21 in the liver, 11 in the lung, 11 in the abdominal cavity and six in other sites. Twenty-two patients with metachronous tumours showed recurrence: 13 in the liver, nine in the lung and one in the abdominal cavity. A greater recurrence rate in the abdominal cavity was observed in patients with synchronous than with metachronous tumours ($P < 0·05$).

In 91 per cent of patients with hepatic recurrence after curative resection, tumours were confirmed within 18 months. No significant differences in the rate of hepatic recurrence were observed according to the factors studied (*Table 2*).

The sites of recurrent tumour in the liver remnant were classified by ultrasonography, CT and/or operative findings. Of ten patients developing tumours at the resection bed, partial resection had been performed in six. Three of these patients might not have developed recurrence if the initial surgery had been more extensive. Seven patients developed tumours in the same lobe. Of six patients undergoing partial resection, two might not have had a relapse if they had undergone lobectomy. Recurrent tumours were found in the contralateral lobe in five patients and in both lobes in 12.

Table 3 summarizes the outcome of patients with five or more tumours. Of ten patients with bilobar metastases, four survived >3 years, including two without relapse. By contrast, five of seven patients with multiple unilobar metastases survived without relapse for >3 years.

Of 17 patients with positive resection margins, lobectomy was performed in seven, left lateral segmentectomy in three and partial resection in seven. Recurrent tumours were confirmed in 16 patients: 11 in the liver and five in extrahepatic organs.

Table 3 *Details of patients with five or more metastases*

Patient no.	No. of metastases	Bilobar metastases	Type of surgery	Follow-up (months)	Status	Recurrence in liver remnant	Extrahepatic recurrence
1	15	+	Right lobectomy plus partial resection (1)	16	Dead	–	–
2	15	+	Right lobectomy plus partial resection (3)	19	Dead	+	–
3	12	+	Partial resection (4)	55	Alive	–	–
4	10	+	Right lobectomy plus partial resection (1)	28	Dead	–	–
5	6	+	Partial resection (6)	7	Dead	–	Abdominal cavity
6	6	+	Partial resection (3)	9	Dead	+	–
7	6	–	Left lobectomy	26	Dead	+	–
8	6	–	Left lobectomy	43	Alive	–	–
9	6	–	Right lobectomy	52	Alive	–	Abdominal cavity
10	5	+	Partial resection (5)	29	Alive	+	Abdominal cavity
11	5	+	Partial resection (4)	39	Alive	+	Abdominal cavity
12	5	–	Partial resection (5)	45	Alive	–	–
13	5	+	Left lateral segmentectomy plus partial resection (2)	56	Alive	–	–
14	5	+	Partial resection (2)	56	Alive	–	Lung
15	5	–	Left lobectomy	117	Alive	–	–
16	5	–	Partial resection (3)	120	Alive	–	–
17	5	–	Partial resection (1)	127	Alive	–	–

Values in parentheses are numbers of partial resections

Discussion

Because of advances in diagnostic technology and hepatic surgery, interest in surgical treatment of metastatic liver tumours has increased. CEA assay and ultrasonography are now used during follow-up after colorectal surgery, and intraoperative ultrasonography can detect hepatic tumours <1 cm in diameter[22]. Hepatic resection has become a safer procedure with a mortality rate[6–12,16,17] <5 per cent and acceptable morbidity[6,8–11]. Perhaps some patients with hepatic metastases are now cured; 5-year survival rates range from 25 per cent[10] to 45 per cent[11].

Adson[23] and Steele and Ravikumar[24] summarized the factors associated with long-term survival. In most series[7,8,13,14,16] the stage of the primary lesion was considered to be an important prognostic factor. This was not confirmed in the present study. The relationship between this factor and survival may be affected by the quality of surgical treatment of the primary lesion and the biological behaviour of the tumour.

As in the present study, others[7,8,10,13,14,16,17] have found no difference between survival rates of patients with solitary and multiple metastases. Seven of 17 of the present patients with five or more tumours survived >3 years without relapse. Iwatsuki *et al.*[8] and Ekberg and colleagues[15], however, reported a poor prognosis in patients with more than three tumours. It is difficult to place an upper limit on the number of metastases that should be resected, because the number may be related to the site and size of tumours. Doci *et al.*[16] concluded that the extent of liver involvement was the most important determinant.

Most authors[8,10,12,14–16] have observed no difference between survival rates in patients with synchronous and metachronous metastases. The higher survival rate of those with metachronous lesions in the present study may be due in part to a lower recurrence rate in the abdominal cavity. This is probably selection bias: in the metachronous group, patients with simultaneous abdominal recurrence were excluded.

In agreement with Hughes *et al.*[13] and Doci and colleagues[16], we believe that any patient with a resectable tumour confined to the liver is a candidate for resection. The present results do not suggest any factor as an absolute contraindication, except the condition of incomplete removal of hepatic tumours. Patients in whom tumours are removed completely can expect long-term survival. Even if they develop recurrence, the prognosis is still superior to that in those who have not undergone surgery[1]. The presence of extrahepatic metastases may be a contraindication, but some may expect long-term survival when extrahepatic tumours are also removed.

Not all the patients with positive resection margins developed hepatic recurrence. Although some may be free from tumour in the liver, this factor is an unreliable prognostic marker.

In most series[6–12,14,15,17] lobectomy was the main procedure. In the present study, 74·8 per cent of procedures were ultrasonographically guided partial resection. The surgical procedure can be evaluated on the basis of hepatic recurrence and complications. The hepatic recurrence rate of 31·8 per cent in the present study is similar to, or better than, those in other series[8,10,12,15,25], and five patients might not have developed recurrence if they had received more extensive surgery. The present mortality rate of 1·8 per cent and morbidity rate of 22 per cent are acceptable, and most complications were minor.

Considering that the current follow-up system makes early detection possible, and that most liver metastases have no satellite deposits, partial resection may be an adequate procedure for many patients. Frequent assessment of the clearance margin using intraoperative ultrasonography can avoid a positive surgical margin.

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Growth rate and percentage hepatic replacement of colorectal liver metastases

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The growth of 32 untreated colorectal liver metastases and hepatic parenchymal volume in 11 patients were studied using planimetry of computed tomographic images. The median percentage hepatic replacement (PHR) of metastases was 0·49 (range 0·09–18·2). At subsequent assessment a median of 72 (range 14–235) days later, metastases were significantly larger with a median PHR of 1·78 (range 0·10–22·9) ($P < 0{\cdot}001$). *To compare the growth of metastases with variable PHR, logarithmic changes of PHR over 100 days were studied. This parameter was shown to be reduced in metastases of larger volume. The median (interquartile range) non-neoplastic hepatic parenchymal volume was found to increase from 1839 (1647–1997) to 2200 (1590–2401) cm*^{3} ($P = 0{\cdot}005$) *as metastatic burden increased. These findings suggest that the growth of colorectal hepatic metastases is more complex than a simple process of hepatic replacement.*

Measurement of the growth rate of hepatic colorectal metastases is of increasing importance because changes in this parameter could be a sensitive measure of the effects of treatment[1]. Tumour growth rate can be assessed by direct measurement of tumour size *in vivo*[2], stathmokinetic techniques[3] and methods involving cell proliferation analysis such as multiparameter flow cytometry to assess 5-bromo-2′-deoxyuridine uptake in neoplastic cells[4].

Havelaar *et al.*[1] estimated the growth rate of two hepatic metastases calculated from the average diameter through the two greatest dimensions as imaged by computed tomography (CT). Finlay *et al.*[5] used a similar technique but considered metastases to be ellipsoid and measured orthogonal dimensions. A comparison of surgically occult and overt colorectal hepatic metastases revealed the latter to grow more slowly[5]. Inaccuracies in the calculation of the tumour volume were likely in these studies because metastases were considered as regular geometric shapes. In addition, the assumption that a change in size of a metastasis is the direct result of neoplastic change may be erroneous: a change in metastasis size may occur as a result of extrahepatic factors. In this study percentage hepatic replacement (PHR) was used as a parameter of metastatic volume in an attempt to minimize extrahepatic effects. PHR was measured by the technique of planimetry using a microcomputer system[6]. Planimetric assessments offer improved accuracy in estimating tumour volume, are sufficiently sensitive to detect small changes in tumour size and can be applied to lesions of irregular shape[7,8].

In a retrospective analysis, the relationships between the PHR of colorectal liver metastases, metastasis growth rate and changes in non-neoplastic hepatic parenchymal volume were investigated in patients in whom sequential CT images of metastases were available and for whom no active treatment was given.

Patients and methods

Patients

Details of patients with colorectal hepatic metastases imaged by more than one CT investigation were retrieved from an audit of CT records of patients for the period 1984–1989.

Computed tomography

A Phillips 2000 tomoscan (Phillips, Eindhoven, Holland) was used to image tumours in all patients using intravenous contrast, a straight gantry angle and a slice thickness of 0·9–1·8 cm.

Percentage hepatic replacement measurements

The technique of planimetry was used to measure PHR from CT hard copy images of the liver and employed a microcomputer system (Deskpro 386N; Compaq, Houston, Texas, USA), customized software, a digitizing tablet and cross-hair cursor (TDS LC series II; Terminal Display Systems, Blackburn, UK). This technique has been described previously[8]. Values of PHR were obtained from measures of metastasis and total liver size.

Metastases

All identifiable metastases ($n = 32$) in 11 patients (five male, six female) were measured; the median volume was 9 (interquartile range (i.q.r.) 3–32) cm^3. Metastases were imaged on two occasions using CT. One metastatic deposit was studied in three patients, two in two patients, three in two patients, four in two patients and five and six metastases in one patient each. No further metastases were identified on the second CT scan.

Calculation of growth rate

The natural logarithm of all measures of PHR was calculated to obtain the 'logical percentage hepatic replacement' (LPHR). This parameter ensures that relative volume changes of metastases with different PHRs can be compared directly irrespective of the initial PHR[9]. To assess growth an arbitrary period of 100 days was adopted. This generated a novel parameter of growth rate, the 100-day change in LPHR, for each metastasis studied.

To assess the relationship between growth rate and PHR, the mean value of the two PHR determinations was used. Hepatic parenchymal volumes were obtained by subtraction from the total liver volume of the volume of metastases.

Statistical analysis

Student's paired *t* test was used to assess changes in PHR and hepatic parenchymal volume.

Results

The median PHR of metastases on initial assessment was 0·49 (i.q.r. 0·14–1·70). On subsequent CT assessment a median of 72 (i.q.r. 47–102) days later the median PHR had risen significantly to 1·78 (i.q.r. 0·41–2·56) ($P < 0{\cdot}001$; *Figure 1*). A plot of metastasis growth rate expressed in terms of change in

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LPHR per 100 days *versus* PHR (*Figure 2*) illustrated that metastases with the largest PHRs had the slower growth. The median (i.q.r.) of the 11 hepatic parenchymal volumes was shown to be significantly increased ($P = 0{\cdot}005$) on subsequent CT assessment in these patients with progressive metastatic disease (from 1839 (1647–1997) to 2200 (1590–2401) cm^3).

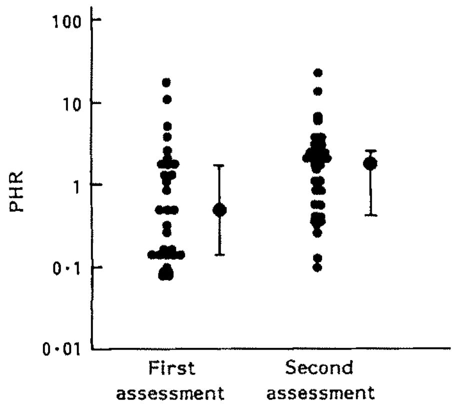

Figure 1 *Percentage hepatic replacement* (*PHR*) *of 32 colorectal liver metastases obtained by planimetry of computed tomographic images taken a median of 72* (*interquartile range 47–102*) *days apart. Bars are median* (*interquartile range*). ($P < 0{\cdot}001$, *Student's paired* t *test*)

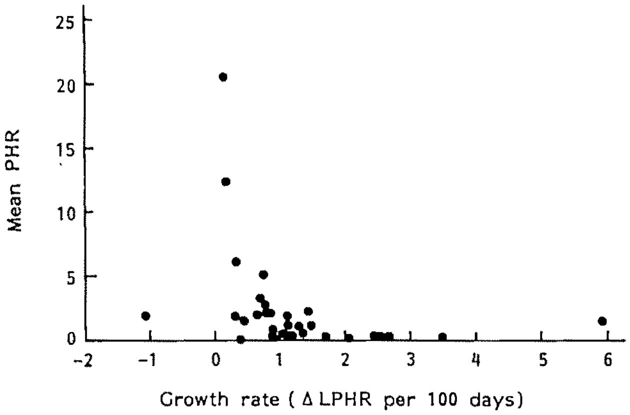

Figure 2 *Growth of 32 colorectal liver metastases expressed as the difference in the natural logarithm between two observations of percentage hepatic replacement* (*PHR*) *over 100 days* (*ΔLPHR per 100 days*) *relative to their mean PHR*

Discussion

Few studies have investigated the natural growth rate of colorectal hepatic metastases (*Table 1*). This is surprising considering colorectal carcinoma is common and hepatic metastases the most important determinant of survival[12].

Finley *et al.*[5] and Havelaar and colleagues[1] assessed the growth of colorectal hepatic metastases in terms of changes in tumour volume with time. These studies differed from the present one, which measured changes in PHR. The use of PHR as a parameter of metastasis volume is an important advance because observed changes in the size of a hepatic metastasis may be the result of extrahepatic factors. PHR represents a ratio between hepatic and tumour volumes such that, if it is assumed that extrahepatic factors affect liver and metastasis volume in equal proportion, errors from such effects can be minimized. A value for the doubling time using PHR as the parameter of tumour size can be calculated from the estimates of liver metastasis growth in this study. These values are presented in *Table 1*; metastases are grouped arbitrarily into those with PHR $\leqslant 3$ and >3, with estimates of volume doubling times from other authors to act as a comparison. The use of doubling time as a measure of tumour growth must be treated with caution to avoid the implication that growth is the direct result of neoplastic cell proliferation alone. The measurement of a change in volume of a radiological abnormality, which in a hepatic metastasis will consist of vascular, stromal and inflammatory elements in addition to neoplastic cells, is likely to be inaccurate compared with techniques that measure the neoplastic component more directly. Taking these factors into consideration the present results fall within a similar range to those of other workers but in particular those of Finlay *et al.*[5], who considered occult and overt metastases which could be compared to the PHR groups in the present study.

The use of PHR is complicated when the growth rates of different-sized metastases are compared. This is because an arithmetic PHR scale cannot express relative changes equally for metastases of different initial PHR. Consider two metastases with initial PHRs of 10 and 20 that double in size; the PHRs will change to 20 and 40 respectively. Over a given time period the larger metastasis would have the steepest growth gradient although the relative changes of both metastases are the same. Tornqvist *et al.*[9] considered this problem theoretically for non-biological applications; they proposed that the natural logarithm of changes in percentages should be adopted and used the term 'logical percentage change' to signify this transformation. The change in LPHR over a period arbitrarily defined as 100 days in the present study can therefore be used

Table 1 *A comparison of doubling times of primary and metastatic colorectal carcinoma*

Reference	Year	Method	No. of metastases	Doubling time (days)
Spratt and Ackerman[10]	1961	Orthogonal diameters	1	636
Welin *et al.*[11]	1963	Orthogonal diameters on barium radiography	375	109
Lokich *et al.*[2]	1981	Orthogonal diameters of pulmonary metastases on chest radiography	4	70
Havelaar *et al.*[1]	1984	Orthogonal diameters on CT		
		Hepatic metastases	6	70
		Intra-abdominal metastases	1	66
		Lymph node metastases	1	62
Finlay *et al.*[5]	1988	Orthogonal diameters of hepatic metastases on CT	29	155 (overt) 86 (occult)
Purkiss and Williams	1993	Planimetry and PHR doubling time of hepatic metastases		
		PHR $\leqslant 3$	28	52
		PHR > 3	4	199

CT, computed tomography; PHR, percentage hepatic replacement to compare directly the growth kinetics of metastases of widely different PHRs.

The results demonstrate that metastases with the smallest PHRs have the fastest growth. This suggests that, if antineoplastic agents acting on the cell cycle are to be applied in this disease, they would be best administered when cell turnover or growth is greatest. The smallest metastases are therefore likely to be the most suitable for treatment.

The finding that non-neoplastic hepatic parenchymal volume expanded as metastatic burden increased is interesting. An increase in hepatic parenchymal volume may occur from such processes as hepatocyte swelling or proliferation. Alternatively, proliferation of non-hepatocyte parenchymal cells such as lymphocytes and tissue macrophages (Kupffer cells) may occur as a response to the progressive neoplastic disease within the liver. An increase in liver volume may also result from changes in the intrahepatic vascular volume as a consequence of systemic extracellular fluid changes or hepatic perfusion. An increased hepatic perfusion index has been observed in patients with hepatic metastases from colorectal carcinoma compared with similar patients without liver involvement[13]. This change in perfusion index could be the result of the rise in hepatic parenchymal volume observed in the present study. An increase in intrahepatic biliary volume could also explain the observed rise in hepatic parenchymal volume as the result of intrahepatic duct obstruction. Alternatively, the expansion of apparently normal liver volume could occur from proliferation of metastatic disease that remains occult. Whatever the explanation, the present results indicate that growth of liver metastases is more complicated than a simple process described by hepatic replacement.

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Elective hepatic resection for benign and malignant liver disease: early results

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Between August 1989 and April 1992, 60 consecutive elective hepatic resections were performed by one surgeon at two hospitals. This personal series was reviewed to determine the early results of elective hepatic resection. There were 17 patients with liver metastases from colorectal cancer, 14 with hepatocellular carcinoma (three with cirrhosis), seven with cholangiocarcinoma, six with carcinoma of the gallbladder plus liver involvement, ten with liver metastases from other sites and six with benign conditions of the liver. Thirty-eight patients underwent major liver resection, seven unisegmentectomy, six bisegmentectomy, four trisegmentectomy and five non-anatomical resection. Total vascular exclusion was used in 50 cases and the Pringle manoeuvre in ten. The mean(s.d.) operative blood transfusion was 990(1260) ml packed red blood cells (range 0–13 units); 17 patients did not receive blood transfusion. There were two operative deaths; non-fatal complications developed in 16 patients. The two deaths were from postoperative liver failure and there was no other hospital death.

Liver resections are increasingly being performed with expanded indications and surgical limits. A better understanding of hepatic anatomy and physiology has improved operative mortality rates over the past few years[1–5]. This is a report on the early results of 60 patients undergoing elective hepatic resection, with particular emphasis on operative strategy. The operative principles include stringent measures to avoid intraoperative blood loss, preservation of functional hepatic parenchyma whenever possible (to allow future repeat resections) and resection along anatomical planes.

Patients and methods

Between August 1989 and April 1992, 60 elective hepatic resections were performed by one surgeon (N.A.H.) at the Hammersmith and Royal Free hospitals. There were 25 men and 35 women with a mean(s.d.) age of 55·2(12·4) (range 18–76) years. The indications for resection are listed in *Table 1*.

Metastases from colorectal cancer and hepatocellular carcinoma (HCC) were the two commonest indications. The type of resection is shown in *Table 2*. Procedures were defined according to the Couinaud[6] anatomical classification of segmental liver anatomy. There were 38 major and 22 minor hepatectomies, which included segmentectomies and non-anatomical resections. Repeat hepatectomies were performed in five patients, with one patient undergoing two repeat resections for metastases from colorectal cancer. Preoperative investigations included full blood count, estimation of serum urea and electrolyte levels, liver function tests, coagulation screen, chest radiography, computed tomography and angiography. Of late, computed tomographic portography has become routine in assessing patients with liver tumours.

Before laparotomy the patient was covered with Thermodrape (Concepts, Texas, USA) and all fluids were administered via a heat-exchange perfusion set to minimize hypothermia. An upper transverse incision with upper midline extension was used to gain access to the abdomen. Strong mechanical retractors (Thompson Surgical Instruments, Illinois, USA) were used to lift the costal margins upward and cephalad to provide full access to the liver. Extension of the incision into the thorax was not necessary. The wound edges were cleaned with povidone–iodine and protected with a wound protector (Steri-Drape; 3M, Leicester, UK). The liver was fully mobilized by taking down the triangular and falciform ligaments. Intraoperative ultrasonography was usually performed to confirm the preoperative findings. The portal triad was dissected and the appropriate portal, arterial and venous branches ligated and transected. The suprahepatic and infrahepatic inferior vena cava (IVC) was then mobilized and slung. A trial dissection of the hepatic veins was performed and, if easy extrahepatic ligation was feasible, this was done by tying the relevant hepatic vein in continuity using a silk ligature. However, this dissection was readily abandoned if it was difficult and posed a potential hazard. In such circumstances dissection of the hepatic veins was left until transection of the parenchyma was almost complete; the hepatic veins were then transected from within the liver parenchyma. The right adrenal vein was ligated in cases where total vascular exclusion was envisaged, and divided to help dissection of the IVC when difficulty was encountered in dissection of the suprahepatic IVC. The phrenic veins were ligated only in cases of low insertion into the IVC. Total vascular exclusion was achieved, in 50 patients, by clamping the inflow portal tract and

Table 1 *Indication for operation in 60 consecutive patients undergoing elective liver resection*

Indication	No. of patients
Liver metastases from colorectal carcinoma	17
Hepatocellular carcinoma	
Normal liver	11
Cirrhotic liver	3
Cholangiocarcinoma	7
Carcinoma of the gallbladder with liver involvement	6
Other liver metastases	10
Benign conditions of the liver	6

Table 2 *Type of liver resection performed in 60 consecutive patients*

Type of resection	No. of patients
Major resection	
Right hepatectomy	12
Extended right hepatectomy	10
Left hepatectomy	15
Extended left hepatectomy	1
Total	38
Segmentectomy	
One segment	7
Two segments	6
Three segments	4
Total	17
Non-anatomical resection	5

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Table 3 *Intraoperative blood loss, blood transfusion requirement, total duration of operation and hospital stay in 60 consecutive patients undergoing liver resection*

	No. of patients	Intraoperative blood loss (ml)	Packed red blood cells transfused (ml)	Total duration of operation (min)	Length of hospital stay (days)
All patients	60	1731(1864)	990(1260)	334(97)	20·2(16·0)
Major resection	38	2108(2022)	1200(1350)	354(94)	22·3(17·0)
Segmentectomy	17	855(599)	480(540)	308(95)	13·2(8·1)
Non-anatomical resection	5	1840(2380)	840(990)	270(80)	28·6(20·2)

Values are mean(s.d.)

Table 4 *Postoperative complications after liver resection in 60 consecutive patients*

Complication	No. of patients
Subphrenic collection	6
Biliary leak	3
Pulmonary embolism	3
Pleural effusion	2
Chest infection	2
Wound infection	2

then the infrahepatic IVC, followed by the suprahepatic cava. A trial clamping for total vascular exclusion was performed for 5 min after intravenous preloading with colloids. Once it had been ascertained that vascular exclusion was well tolerated, the clamps were applied in the sequence described.

The margins of resection were marked on the liver surface with an argon laser diathermy coagulator (Valleylab, London, UK). This was also used to transect the liver parenchyma. Biliary, arterial and venous branches were identified during the resection and sutured with 3/0 polypropylene. The argon coagulator provided adequate haemostasis for the smaller vascular branches. In some cases the edges of the cut surface of the liver were approximated with 1/0 polypropylene to ensure haemostasis. The falciform ligament was reconstructed with 2/0 polyglactin stitches to prevent excessive rotation of the liver after hepatectomy. Closed drainage with silicone tubes was established only if the transected liver surface was deemed not absolutely haemostatic or after bilioenteric anastomosis.

During the immediate postoperative period, patients were nursed in the intensive care unit for one night, and returned to the surgical ward the following day. Prophylactic antibiotics (metronidazole and cefuroxime) were given at induction and for 48 h after operation. In patients with cirrhosis or abnormal coagulation, aprotinin was used (2×10^6 units at induction and 500 000 units h^{-1} during the procedure) in an attempt to diminish fibrinolysis. Alprostadil (prostaglandin E_1; Upjohn, Crawley, UK) was also given routinely in a dose of 0·2 $\mu g\, kg^{-1}\, h^{-1}$ (starting at induction and continued for 24 h) to protect the liver from reperfusion injury following total vascular exclusion or Pringle's manoeuvre.

Results

Two patients died (30-day mortality rate 3 per cent). One patient, a 66-year-old man, succumbed from a chest infection 2 weeks after left hepatectomy for HCC in a cirrhotic liver. The other patient, a 40-year-old woman, developed liver failure after extended right hepatectomy for Caroli's disease of the liver. There was no other in-hospital death. There was one intraoperative complication, in a patient who sustained a tear of the IVC during mobilization of the veins. There was no air embolus and the tear was promptly repaired. Intraoperative blood loss, blood transfusion requirements, operating time and hospital stay are shown in *Table 3*. Seventeen patients did not receive blood transfusion. Of these, seven had a major resection, eight a segmentectomy and two a non-anatomical resection.

There were 18 postoperative complications in 16 patients (27 per cent), as shown in *Table 4*. Complications developed in three patients following minor resection and 15 complications developed in 13 patients after major resection. Reoperation was necessary for bleeding in two patients (3 per cent). The first was because of bleeding from a mesenteric vessel after simultaneous right hemicolectomy. The second was 14 days after resection of segments II and III, because of a slipped ligature from the distal end of the left hepatic artery.

The mean postoperative hospital stay was 20·2 days. In 50 cases where total vascular exclusion was used, the mean(s.d.) ischaemia time was 41·6(24·8) (range 25–70) min. The Pringle manoeuvre alone was used in ten patients early in the series, with a mean(s.d.) clamping time of 32·3(16·3) (range 15–30) min. *Table 5* shows preoperative and postoperative values for prothrombin time, and aspartate transaminase and serum bilirubin concentrations.

Discussion

These results suggest that liver resection can be performed with low operative morbidity and mortality rates. Two important surgical principles should be emphasized: obtaining an optimum exposure and the avoidance of excessive intraoperative blood loss. The upper transverse incision with midline extension and fixed retraction system provide a constant good exposure and hence safer surgery. The authors now routinely mobilize the IVC and portal structures to facilitate total vascular exclusion. This was done in 83 per cent of the present cases. As operative death during hepatectomy is usually caused by exsanguination secondary to hepatic vein or vena cava injury[7–9], establishing control of the vascular structures provides the surgeon with adequate control of a potentially disastrous situation. There was only one injury to the IVC in 50 patients, which was promptly repaired under total vascular exclusion. The above routine dissection allows familiarity and enables the surgeon to transect the hepatic parenchyma with

Table 5 *Laboratory data before and after liver resection*

	Before operation	Time after operation				
		Day 1	Day 2	Day 5	Day 10	Day 15
Prothrombin time (s)	13·3(1·3) (11·2–17)	19·3(3·8) (13·6–27·8)	20·1(6·1) (13–41·7)	17·4(3·9) (13·3–29·7)	15·7(2·7) (12·8–23)	14·6(2·2) (12–20·5)
Aspartate transaminase (units l^{-1})	96·7(169·8) (14–760)	386·5(322·4) (38–1120)	278·8(298·5) (47–1082)	80·9(50·6) (23–242)	72·1(63) (16–321)	73·2(79·2) (18–394)
Serum bilirubin (μmol l^{-1})						
Non-icteric patients	10·6(3·3) (4·8–18)	63·3(85) (8–335)	64·8(5·6) (13–205)	39·5(29) (10–115)	23·7(13) (11–64)	18·6(8·6) (11–34)
Icteric patients	120·0(100·6) (29–324)	134·4(106·3) (33–316)	137·4(99·3) (33–273)	138·0(104·4) (18–301)	117·5(118·2) (24–318)	78·4(90·5) (21–275)

Values are mean(s.e.m.) (range)

minimal intraoperative blood loss. It has been shown that operative blood loss is the most decisive factor in determining the short-term prognosis in patients undergoing hepatectomy[8,10]. Furthermore, the risk of post-transfusion viral infection (hepatitis and cytomegalovirus) is reduced by minimal infusion of blood products. Blood transfusion itself is an independent factor contributing to multiple organ failure[11]. Total vascular exclusion might enable the surgeon to be more radical in resecting posteriorly situated neoplastic lesions, and can be beneficial in cases where dissection of the hepatic veins becomes difficult and hazardous. It is often warranted in posteriorly situated tumours but is not necessary for anteriorly placed lesions[11,12]; in the latter case, Pringle's manoeuvre is sufficient. Total vascular exclusion proved to be a safe procedure for tumours that were centrally placed and invaded the vena cava. It may extend the resectional indication for conditions that would otherwise have been deemed irresectable. Total vascular exclusion may occasionally help the surgeon to obtain a radical margin but is certainly not a prerequisite in the more common standard procedures. To make the vascular exclusion effective, right adrenal vein drainage in the IVC has to be controlled. This should be achieved by its ligation in continuity, its division or oblique application of the infrahepatic IVC clamp so that it is placed above its entrance in the IVC. In the present study total vascular exclusion was applied in 50 resections, of which only 38 were major. In the remaining 12, total vascular exclusion was applied because the resection involved removal of posteriorly situated liver tissue or central lesions near the IVC that were resected segmentally or non-anatomically. Hepatectomy is best performed in optimum conditions with continuous vascular exclusion, without any interruption. A prolonged warm ischaemia time of <1 h has been found to be safe for the normal human liver, and is not associated with long-term sequelae[12,13].

There were two deaths in this consecutive series of 60 liver resections. The first was the seventh patient in the series, who died from pneumonia and liver failure (Child's grade B) following left hepatectomy for HCC complicating liver cirrhosis. This highlights the potential problem of liver insufficiency in patients with poor hepatic function. The second death was the 11th patient operated on in the series. She underwent extended right hepatectomy for Caroli's disease and died from liver failure secondary to portal vein injury. She was deprived of portal blood supply following ligation of the right branch of the portal vein. Retrospective assessment of the portogram showed lack of bifurcation of the portal vein. This occurs in 1 per cent of the population, where the portal vein continues as the right branch entering the right side of the liver, and then syphons to the left to supply the left liver. After that case, detailed hepatic portography is now carried out in all patients undergoing major hepatectomy.

Postoperative bleeding requiring reoperation was not a significant problem in the present series. One patient required relaparotomy for bleeding unrelated to the liver resection. Another bled for 14 days after resection of segments II and III, owing to a slipped ligature from the distal end of the left hepatic artery. Biliary fistula developed in three patients; all lesions closed spontaneously without further operation. One leak occurred in a patient after repeat resection for HCC following resection of a recurrence near the liver hilum. Two further leaks occurred in patients after excision of cholangiocarcinoma of the hilum, confirming that the risk of bile leakage is higher when a procedure involves the main bile ducts[9]. Six patients developed postoperative subphrenic collections, of which five followed major hepatic resection. All were drained percutaneously under ultrasonographic control, with complete resolution within a 2-week period.

In conclusion, elective hepatic resection can be performed with minimal morbidity and mortality. With improved techniques and postoperative care, indications for liver resection should widen. Patients should be followed carefully after resection, with the possibility of future re-exploration in mind. This will, it is hoped, improve survival in those with primary and secondary liver tumours, as other methods of treatment do not seem to offer better prospects at present.

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Role of serum endotoxin and antiendotoxin core antibody levels in predicting the development of multiple organ failure in acute pancreatitis

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It has been proposed that endotoxin contributes to the development of multiple organ failure (MOF) in acute pancreatitis. Endotoxaemia is transient and may not be detected by intermittent blood sampling. By contrast, not only can changes in the patient's endogenous antiendotoxin core antibody pool persist for many days, but depletion of this pool may be a key event in determining the physiological significance of endotoxaemia. A series of 33 patients with acute pancreatitis had daily measurement of Acute Physiology Score (APS) and levels of C-reactive protein, interleukin 6, endotoxin, immunoglobulin (Ig) G and IgM antiendotoxin core antibodies, and prospective documentation of complications. Endotoxin was detected in the serum of 13 patients, while a significant change in levels of endogenous antiendotoxin core antibodies was detected in all those with severe pancreatitis and in 28 overall. MOF developed in seven patients, five of whom died. The combination of a rising APS over the first 48 h of admission and a significant fall in endogenous IgG antibody level was observed in all patients who developed MOF (seven of seven), but in only one of 16 without MOF (P = *0·00003; overall predictive value 91 per cent). This study suggests that measuring the initial trend in APS and the concentration of endogenous IgG antiendotoxin core antibody provides a means of identifying patients with acute severe pancreatitis who are at high risk of developing MOF. This group might benefit from passive immunotherapy with antiendotoxin antibodies.*

Endotoxin is considered to play an important role in the pathophysiology of the sepsis syndrome and multiple organ failure (MOF). However, these clinical syndromes may develop when bacteria cannot be cultured from peripheral blood[1,2] and when endotoxin is undetectable[3]. It is known that endotoxaemia induces complement and coagulation activation, the generation of vasoactive kinins and the stimulation of mononuclear phagocytes to produce cytokines including interleukin (IL) 1, IL-6 and tumour necrosis factor (TNF). These cytokines are also produced as a result of pancreatic inflammation[4,5]. Among the many effects of such cytokines is the stimulation of synthesis of hepatic acute-phase proteins, including C-reactive protein (CRP), which has been used as a marker of the severity of acute pancreatitis[6–8]. In addition, parenteral administration of TNF has been shown to induce changes consistent with MOF in animal models.

There is some evidence to suggest that MOF occurs more frequently in patients with acute pancreatitis who have detectable circulating levels of endotoxin[9] and that the degree of endotoxaemia may correlate with the severity of acute pancreatitis and the development of MOF[10,11]. It is suggested that prevention of endotoxaemia or neutralization of its effects before the potentially deleterious release of the cytokine mediators might prevent or ameliorate consequent MOF.

The availability of monoclonal antibodies, including those directed against endotoxin, TNF and the interleukins, has made specific intervention possible at several points in the complex chain of humoral events associated with the development of MOF. Several clinical studies have already been reported, suggesting that passive immunization with antiendotoxin antibodies may reduce morbidity and mortality rates in selected groups of patients with major sepsis[12–14]. A significant reduction in mortality rate has been reported both in primates with Gram-negative sepsis using antibodies to TNF[15] and in endotoxaemic rabbits using an IL-1 receptor antagonist[16]. However, it is not known whether this type of treatment might be effective in reducing the mortality rate associated with MOF in patients with acute severe pancreatitis.

The present study was designed to evaluate the degree of endotoxaemia in patients with acute pancreatitis, both by direct measurement of serum endotoxin levels and by measuring changes in the antiendotoxin core antibody concentration. The relationship between endotoxaemia and levels of antiendotoxin antibodies, IL-6 and CRP was examined. Using these markers of the humoral events underpinning acute pancreatitis, a practical method was developed for identifying patients with severe pancreatitis who were at high risk of MOF and who might benefit from early antiendotoxin or anticytokine therapy.

Patients and methods

A prospective series of 33 patients with acute pancreatitis admitted to The Royal Infirmary between April 1990 and July 1991 was studied. The series was not consecutive because some patients (fewer than ten) with mild disease were rapidly discharged from hospital. The diagnosis of acute pancreatitis was established by the presence of characteristic abdominal pain accompanied by a serum amylase concentration of >1000 units/l (Phadebas; Pharmacia Diagnostics, Uppsala, Sweden; normal range 70–300 units/l). Approval for the study was granted by the ethical committee of the Lothian Health Board and informed consent obtained from all patients.

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The severity of pancreatitis was scored within 48 h of admission using the modified Glasgow method described by Blamey *et al.*[17] and monitored on a daily basis using the Acute Physiology Score (APS) component of the Acute Physiology and Chronic Health Evaluation score[18]. Blood samples were taken daily for assessment of the severity and progress of pancreatitis.

The patient's clinical course was monitored closely and any investigation, intervention or adverse clinical event documented. The number of days in hospital was recorded.

Local complications were defined as follows: (1) pancreatic necrosis was diagnosed as defined areas of low or absent enhancement on rapid-bolus contrast-enhanced computed tomography (CT)[19], or visually identified necrosis at the time of necrosectomy or on histological examination of a resected specimen; (2) pancreatic pseudocyst was defined as a collection of fluid >5 cm in diameter seen on ultrasonography or CT, or at the time of laparotomy, but was considered a complication only if it persisted for >6 weeks or required drainage; (3) pancreatic abscess was diagnosed when a positive bacteriological culture resulted from pus obtained by percutaneous aspiration or at the time of operative drainage; and (4) pancreatic ascites and pleural effusion were noted on ultrasonography or CT but were not considered a complication unless they required drainage.

Systemic complications relating to acute pancreatitis were defined as follows: (1) pneumonia was diagnosed by the presence of a fever >38°C with clinical and/or radiological evidence of pulmonary consolidation; (2) circulatory failure or shock was diagnosed when inotropic support was required or when the systolic blood pressure was <100 mmHg and heart rate >100 beats/min after an intravenous fluid load of 2 litres; (3) respiratory failure was diagnosed when mechanical ventilation was considered necessary; and (4) renal failure was diagnosed when patients required dialysis or when creatinine levels exceeded 300 μmol/l in the face of normal preoperative renal function. MOF was diagnosed when at least two organ systems were involved.

Blood sampling protocol

Samples of venous blood (10 ml) were withdrawn into plain glass tubes from all patients twice daily for the first 2 days of admission, and then on a daily basis for at least 5 more days. Blood was centrifuged and the supernatant stored at −70°C for subsequent batch analysis.

Endotoxin and antiendotoxin core antibody assays

The level of endotoxin was determined using a kinetic chromogenic *Limulus* amoebocyte lysate method based on the endotoxin-specific Endospecy assay (Seikagaku, Tokyo, Japan). The limit of detection was ≤5 pg/ml. Concentrations of endogenous antiendotoxin core antibodies (immunoglobulin (Ig) M and IgG) to core glycolipid antigens were measured by a direct enzyme-linked immunosorbent assay (ELISA) described by Barclay *et al.*[20]. Normal ranges for these antibodies were established from a study of more than 1000 normal blood donors: the median IgG antiendotoxin core antibody concentration was 48·9 (10th to 90th percentile 21·3–133·1) units/ml and the median IgM antiendotoxin core antibody concentration 149·4 (10th to 90th percentile 73·2–446·7) units/ml.

Acute-phase response

The acute-phase response was documented by assaying CRP (Abbott Diagnostics, Maidenhead, UK). The level of IL-6 was measured by an indirect sandwich ELISA (British Biotechnology, Abingdon, UK) with a limit of detection of 15 pg per ml serum.

Statistical analysis

All results are expressed as mean(s.e.m.). Groups were compared by Student's *t* test for continuous variables and by Fisher's exact two-tailed test for categorical variables.

Results

A total of 33 patients (24 men, overall median age 58 (range 21–90) years) were studied. Eight of these patients were referred from other units within the hospital and eight from other hospitals in Edinburgh. This pattern of referral meant that the majority of patients had severe disease and that in some cases blood sampling was delayed from the onset of disease. The aetiology of acute pancreatitis was apparent in 31 patients: gallstones in 22, alcohol in eight and endoscopic retrograde cholangiopancreatography in one.

Patients were divided into two groups according to the modified Glasgow pancreatitis severity score: those with predicted mild pancreatitis (score <3, $n = 10$) and those with a predicted severe disease (score $\geqslant 3$, $n = 23$). The distribution of severity of pancreatitis according to this scoring system is shown in *Figure 1*. The clinical details of the patients are shown in *Table 1*. Those with predicted severe pancreatitis were significantly older ($P < 0{\cdot}05$) but there was no significant difference between the two groups in terms of sex distribution or aetiology of the pancreatitis. Patients with predicted severe pancreatitis had a significantly higher initial ($P < 0{\cdot}005$) and peak ($P < 0{\cdot}005$) APS, and this group included a higher proportion of patients with a rising APS during the first 48 h of admission ($P = 0{\cdot}012$; *Table 1*).

The clinical outcome is shown in *Table 2*. Patients with predicted severe pancreatitis had a higher overall complication rate ($P = 0{\cdot}009$) and a longer hospital stay ($P < 0{\cdot}01$). There was a higher incidence of local pancreatic complications, systemic complications, MOF and death, but these differences were not statistically significant. MOF developed in seven patients with severe pancreatitis, of whom five died, giving a mortality rate for MOF of 71 per cent.

Endotoxaemia

Endotoxaemia was detected in only 13 of the 33 patients, ten of whom had predicted severe pancreatitis. No correlation was found between the degree of endotoxaemia and the severity of pancreatitis or subsequent clinical outcome.

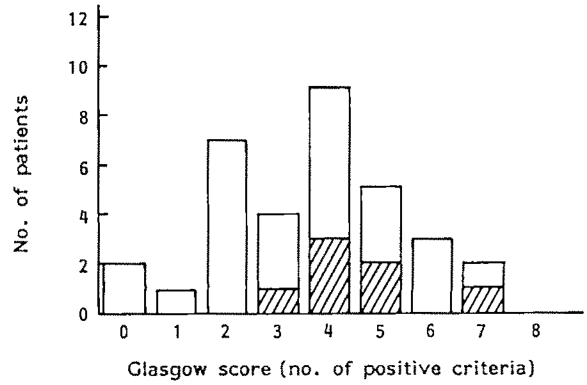

Figure 1 *Severity of acute pancreatitis, determined by the modified Glasgow score, for patients with mild* (n = *10*) *and severe* (n = *23*) *disease.* ■, *Patients who developed multiple organ failure*

Table 1 *Details of patients with predicted mild and severe pancreatitis*

	Mild pancreatitis ($n = 10$)	Severe pancreatitis ($n = 23$)	P
Age (years)*	44(6)	63(3)	<0·05†
Sex ratio (M:F)	6:4	18:5	n.s.‡
Aetiology			
Gallstones	5	17	n.s.‡
Alcohol	5	3	
Endoscopic retrograde cholangiopancreatography	0	1	
Idiopathic	0	2	
Severity			
Glasgow score*	1·3(0·2)	3·9(0·2)	<0·0001†
Acute Physiology Score			
Initial*	0·7(0·6)	4·2(0·8)	<0·005†
Peak*	1·8(0·7)	7·9(1·1)	<0·005†
Trend (first 48 h)			
Falling	10	12	0·012‡
Rising	0	11	

*Values are mean(s.e.m.). †Student's *t* test; ‡Fisher's exact two-tailed test; n.s., not significant

Antiendotoxin core antibody responses

Changes in serum IgM and IgG antiendotoxin antibody concentration are shown in *Table 3*. On admission, the endogenous IgM antiendotoxin core antibody concentration was within the normal range in nine of ten patients with predicted mild pancreatitis, but was depleted (<10th percentile) in 17 of 23 with predicted severe pancreatitis (P = 0·00009; *Table 3*). All patients with severe pancreatitis had depletion and/or a significant fall (>50 per cent decrease in concentration to below the median value) in IgM antibody concentration during the course of the illness compared with only four of ten with mild disease. The IgM antibody concentration was noted to rise subsequently (>50 per cent increase in concentration to above the median value) in four of 23 patients with severe pancreatitis but in none with mild disease.

On admission, the endogenous IgG antiendotoxin core antibody concentration was within the normal range in nine of ten patients with predicted mild pancreatitis. In the 23 patients with predicted severe pancreatitis, the IgG antibody level on admission was significantly depleted (<10th percentile) in four, within the normal range in 13 and significantly raised (>90th percentile) in six. The IgG antibody concentration fell significantly (>50 per cent decrease in concentration to below the median value) in nine patients and became depleted (<10th percentile) in seven with predicted severe pancreatitis. These changes were not found in patients with predicted mild pancreatitis. The IgG antibody concentration was noted to rise subsequently (>50 per cent increase in concentration to above the median value) in six patients with severe pancreatitis. No significant correlation was found between IgM or IgG antiendotoxin antibody concentration and total serum immunoglobulin concentration.

Interleukin 6 and the acute-phase response

No significant correlation was found between peak IL-6 and CRP concentrations (r^2 = 0·032). The IL-6 concentration was maximal on day 3, preceding the peak CRP concentration by 24–48 h. Patients with predicted severe pancreatitis had a greater IL-6 response than those with predicted mild disease (twofold increase in the area under the curve of sequential measurements of IL-6 concentration), although there was no significant difference between the mean daily concentrations of the two patient groups. The mean(s.e.m.) peak IL-6 concentration was significantly higher (P < 0·05) in patients with predicted severe pancreatitis (387(89) pg/ml) than in those with predicted mild disease (130(50) pg/ml). The peak IL-6 concentration appeared to relate to the severity of subsequent complications (*Figure 2*), although this was not of predictive value for individual patients.

Patients with predicted severe pancreatitis had a more marked acute-phase response than those with predicted mild disease (fourfold increase in the area under the curve of sequential measurements of CRP concentration; *Figure 3*). The mean(s.e.m.) peak CRP concentration (119(33) mg/l), which occurred on the fourth day after the start of predicted mild pancreatitis, was significantly lower (P < 0·001) than the peak that occurred on day 5 in patients with predicted severe disease (219(19) mg/l).

Table 2 *Clinical outcome of patients with predicted mild and severe pancreatitis*

	Mild pancreatitis (n = 10)	Severe pancreatitis (n = 23)	P
Morbidity			
Complications (overall)	1	14	0·009†
Pancreatic complications	1	10	0·11†
Pseudocyst	1	7	0·38
Necrosis	0	8	0·07†
Abscess	0	3	0·54†
Systemic complications	1	10	0·11†
Multiple organ failure	0	7	0·07†
Mortality	0	5	0·29†
Hospital stay (days)*	9·8(2·1)	35·1(7·5)	<0·01‡

*Values are mean(s.e.m.). †Fisher's exact two-tailed test; ‡Student's t test

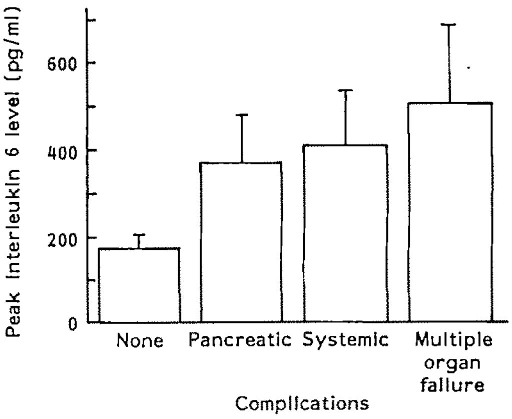

Figure 2 *Peak interleukin 6 concentration in patients who developed no complications* (n = *18*), *local pancreatic complications* (n = *11*), *systemic complications* (n = *11*) *and multiple organ failure* (n = *7*). *Values are mean(s.e.m.)*

Table 3 *Changes in immunoglobulin M and G antiendotoxin antibody response in patients with predicted mild and severe pancreatitis*

	Immunoglobulin M antibody			Immunoglobulin G antibody		
Antibody level	Mild pancreatitis (n = 10)	Severe pancreatitis (n = 23)	P*	Mild pancreatitis (n = 10)	Severe pancreatitis (n = 23)	P*
Falling (>50% decrease to below median value)	3	4	n.s.	0	9	0·03
Depleted (<10th percentile)						
On admission	0	17	0·00009	0	4	n.s.
At any stage	4	23	0·00019	0	7	n.s.
Rising (>50% increase to above median value)	0	4	n.s.	1	6	n.s.
Raised (>90th percentile)						
On admission	1	0	n.s.	1	6	n.s.
At any stage	1	1	n.s.	1	6	n.s.

*Fisher's exact two-tailed test; n.s., not significant

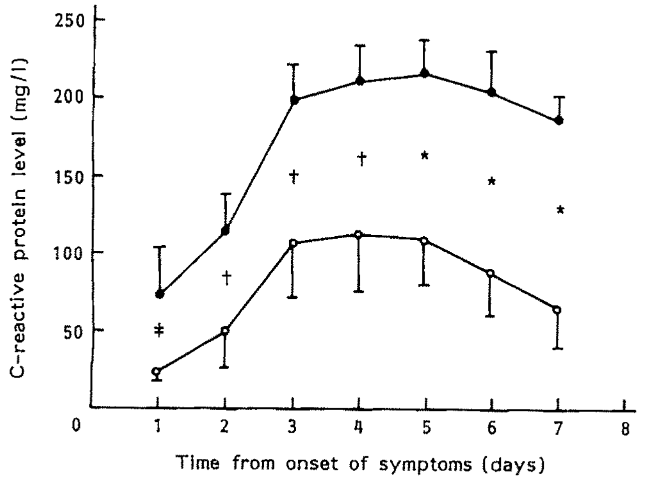

Figure 3 *Sequential C-reactive protein concentration in ten patients with predicted mild* (o) *and in 23 with predicted severe* (●) *pancreatitis. Values are mean(s.e.m.).* *P < 0·01; †P < 0·05; ‡P *not significant* (*mild* versus *severe pancreatitis, Student's* t *test*)

Table 4 *Prediction of multiple organ failure in patients with predicted severe pancreatitis* (*Glasgow score* ⩾*3*)

	Severe pancreatitis with or without rising APS ($n = 23$)	Severe pancreatitis plus rising APS with or without falling IgG* ($n = 11$)
Acute Physiology Score		
Rising	11	11
Falling	12	0
IgG antiendotoxin antibody level		
Rising	—	3
Falling*	—	8
Multiple organ failure	7	7
Prediction of multiple organ failure		
Sensitivity	7 of 7 (100)	7 of 7 (100)
Specificity	12 of 16 (75)	3 of 4 (75)
Positive predictive value	7 of 11 (64)	7 of 8 (88)
Overall predictive value	19 of 23 (83)	10 of 11 (91)

APS, Acute Physiology Score; Ig, immunoglobulin. * >50% decrease in antibody level to below median value and/or <10th percentile. Values in parentheses are percentages

Prediction of multiple organ failure and death

All seven patients who went on to develop MOF were predicted to have severe pancreatitis (Glasgow score ⩾3) and an APS that increased over the first 48 h of admission. Of the 16 patients with predicted severe pancreatitis who did not develop MOF only four had similar characteristics. Combining the modified Glasgow score with the early trend in APS predicted MOF with an overall predictive value of 83 per cent (*Table 4*).

All seven patients who went on to develop MOF had an APS that increased over the first 48 h of admission and a significant fall (depletion to <10th percentile and/or >50 per cent reduction to below the median value) in IgG antibody concentration. Of the 16 patients with predicted severe pancreatitis who did not develop MOF, only one had similar characteristics ($P = 0{\cdot}00003$). Combining the modified Glasgow score, the early trend in APS and a significant fall in IgG antibody concentration further enhanced the prediction of MOF, to an overall predictive value of 91 per cent (*Table 4*).

Discussion

Endotoxaemia may result from the translocation of endotoxin from the gut lumen, with subsequent passage through the portal circulation (and the hepatic reticuloendothelial system) into the systemic circulation. Following acute injury, gut barrier function may fail for several reasons, including splanchnic hypoperfusion and oxygen free radical reperfusion injury[2,21–24], all of which may be relevant in the patient with acute pancreatitis. In the present study, systemic endotoxaemia was found in 39 per cent of patients. However, the incidence of endotoxaemia may have been much higher but not detected owing to the ethical constraints that prevent repeated blood sampling to detect intermittent peaks of endotoxin.

Healthy volunteers have been found to have antibodies that react with the core glycolipid region of endotoxin from a wide variety of Gram-negative bacteria. During endotoxaemia, the circulating levels of such antibodies, particularly those specific for the endotoxin inner core, are reduced in comparison with the individual's stable level, apparently as a result of binding to endotoxin and subsequent removal from the circulation[20]. In the present study, the serum concentration of IgM antiendotoxin antibodies fell in all patients with predicted severe pancreatitis, a change that was independent of any alteration in the total serum immunoglobulin concentration. One mechanism to account for such a change would be the specific binding of endotoxin and the subsequent removal of complexes from the intravascular compartment. If this were the case then the data would suggest that significant exposure to endotoxin had occurred in all patients with severe disease. In relation to the timing of such endotoxaemia, it should be noted that the fall in endogenous IgM antiendotoxin core antibody concentration occurred very early after the onset of pancreatitis, before admission to hospital in 17 of 23 patients with predicted severe disease. However, no correlation was found between the changes in IgM antiendotoxin antibody concentration and clinical outcome.

By contrast, the serum IgG antiendotoxin antibody concentration fell in only nine of the 23 patients with predicted severe pancreatitis. Such a difference might reflect the fact that IgM class antibodies are pentamers of high molecular weight and have a smaller volume of distribution than those of the IgG class. Thus, for the same degree of endotoxaemia, and assuming a similar and constant rate of synthesis for both antibodies, IgM class antibodies might be affected more than those of the IgG type. The finding that all seven patients who developed MOF had a significant fall in IgG class antiendotoxin antibody levels suggests that depletion of the IgG antiendotoxin antibody pool is physiologically significant. Such a fall occurred in only one patient who did not develop these complications. This association could be explained by low antibody concentrations allowing increased exposure to free endotoxin and hence enhanced activation of the systemic responses (e.g. the cytokine cascade) that have been linked to the development of MOF. These findings are similar to those in a study of patients with Gram-negative septicaemia, in which a significant decrease in IgG antiendotoxin antibody binding activity was found in those who did not survive[14].

The initially raised levels of endogenous IgG antiendotoxin core antibody (>90th percentile) observed in six of the 23 patients with predicted severe pancreatitis probably reflects previous exposure to significant levels of endotoxin. Moreover, the secondary rise in endogenous IgG antiendotoxin core antibody concentration (to >90th percentile), observed in a further six patients with predicted severe pancreatitis, might result from repeated or prolonged exposure to endotoxin. This increase in IgG antibody concentration was not associated with a worse clinical outcome.

Endotoxin is a potent inducer of IL-1 and TNF *in vivo*[25], and these cytokines induce macrophages to produce IL-6. IL-6 has a direct role in the terminal differentiation of the immunoglobulin-secreting B cells and is also an important helper factor in primary antigen receptor-dependent T cell activation and subsequent proliferation of activated T cells[26]. IL-6 is also a major regulator of the acute-phase response in human hepatocytes[26], inducing the synthesis of a full range of acute-phase proteins including CRP.

In the present study, the rise in level of IL-6 appeared to be related to the severity of subsequent complications, and has previously been shown to correlate with the magnitude of tissue damage[27]. The poor correlation between the serum peaks of IL-6 and CRP ($r^2 = 0{\cdot}032$) has been noted previously[27] and may simply reflect the fact that serum levels of IL-6 are a poor indication of IL-6 concentration at the physiologically active site in the liver. In the present study, there was a striking temporal relationship between the IL-6 and CRP concentrations in the majority of patients. The serum concentration of IL-6 peaked 24–48 h before the peak CRP concentration in 19 of the 23 patients with predicted severe pancreatitis. This delay is of the same order as the 20–30-h interval noted by others[5,28]. Because of sampling inadequacy, the remaining four patients with severe pancreatitis did not have discernible CRP and IL-6 peak concentrations.

Modulation of the cytokine-mediated acute-phase response has been attempted in a number of experimental models. In this context, non-specific treatment with steroids[29] and prostandoids[30] has been studied extensively. Specific intervention with a range of monoclonal antibodies directed against endotoxin and its related cytokines is now possible. Supplementation of intrinsic immunity by the passive administration of antiendotoxin antibodies before or during endotoxaemia, and before the phase of cytokine release, might result in prevention or more rapid resolution of endotoxaemia and a reduction in the incidence of MOF and death[20]. In a recent study, a human monoclonal IgM antiendotoxin antibody was administered to patients with sepsis caused by presumptive Gram-negative bacteraemia with no overall reduction in mortality rate[12]. Although subsequent analysis revealed a significant reduction in 28-day mortality rate in a group of patients later proven to have Gram-negative bacteraemia, the study did not indicate how to preselect such patients. At present, the role of adjunctive immunotherapy in the prevention and/or treatment of MOF resulting from endotoxaemia remains undefined.

It is probable that the patients likely to benefit from passive immunization with monoclonal antiendotoxin antibody are those in whom the antibody pool has become depleted as a result of ongoing exposure to endotoxin. Furthermore, the timing of such intervention might be critical, to prevent activation of the cytokine cascade. Such intervention would, therefore, require a rapid method to identify patients at most risk of MOF. The antiendotoxin ELISA used in the present study can be performed within a matter of hours, so suggesting a method for identifying such patients within the first 48 h of admission. Patients with predicted severe pancreatitis (Glasgow score $\geqslant 3$), a rising APS within the first 48 h of admission and either IgG antiendotoxin core antibody depletion or > 50 per cent fall in antibody level to below the normal median value have the highest risk of MOF and are most likely to benefit from immunotherapy.

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Improved glucose metabolism after subtotal pancreatectomy for pancreatic cancer

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Diabetes occurs frequently in patients with pancreatic cancer. To investigate the impact of tumour removal, seven patients were studied before and after 85 per cent subtotal pancreatectomy for adenocarcinoma of the pancreas. The frequency of diabetes was determined by the oral glucose tolerance test. Fasting levels of C peptide and insulin were measured in plasma, and insulin secretion was investigated by hyperglycaemic glucose clamp and glucagon stimulation. Six of the seven patients were diabetic before surgery and four required insulin treatment. Improvements in diabetic status and glucose metabolism were found in all seven patients after operation, as demonstrated by increased glucose metabolic capacity during hyperglycaemia. This occurred despite a postoperative reduction in insulin secretion and is explained by the observed augmentation of whole-body insulin sensitivity after surgery. A diabetogenic factor may be produced by pancreatic adenocarcinoma that may be responsible, directly or indirectly, for the high frequency of diabetes in patients with pancreatic cancer.

The majority of patients with pancreatic cancer die within 1 year of diagnosis, and the 5-year survival rate is less than a few per cent[1]. There are no accurate methods for early diagnosis or screening[1,2]. The tumour is frequently beyond surgical resectability or has metastasized when symptoms first appear. Late diagnosis undoubtedly contributes to the early mortality[1], and non-surgical treatment is not successful[1,2].

Cachexia and other metabolic disorders, such as diabetes, are often identified before the diagnosis of pancreatic adenocarcinoma[3]. At the time of diagnosis, up to 80 per cent of patients have impaired glucose tolerance or diabetes[4–6], and the diabetic state can precede the diagnosis by months or years[5,7]. The reason for the high frequency of diabetes is still not known[4,7,8]. An increased fasting level of insulin and an impaired insulin secretory response to hyperglycaemia in patients with diabetes and pancreatic cancer have been reported[4,5]. A reduced number and an altered function of the β cells have been proposed as explanations[9], but other studies[10,11] have failed to confirm this hypothesis. Impaired action of insulin and decreased peripheral insulin sensitivity in patients with pancreatic cancer indicate that factors other than the rate of insulin secretion may be involved[4,5,12,13]. A specific diabetogenic factor in pancreatic cancer has been suggested[4].

This study evaluates the possibility that pancreatic adenocarcinoma exerts a specific diabetogenic effect. Glucose metabolism before and after surgery was investigated in patients with pancreatic cancer to evaluate the effect of tumour removal on glucose metabolism, especially diabetic status, insulin secretion and glucose metabolic capacity.

Patients and methods

Patient characteristics

Seven consecutive patients undergoing subtotal pancreatectomy for pancreatic adenocarcinoma were studied before and 3 months after surgery. Clinical characteristics are shown in *Table 1*. All patients lost weight after the operation, but their weights were static at the time of postoperative investigation. The tumour size ranged from 2·2 to 3·7 (median 3·0) cm. All tumours were located in the head of the pancreas and there was no evidence of metastases before or during surgery. The tumour was highly differentiated in one patient, moderately differentiated in four and poorly differentiated in two. No major postoperative complication occurred in any patient. The hospital stay after surgery ranged from 18 to 26 days. At the time of postoperative investigation there were no signs of recurrence on clinical and ultrasonographic examinations. The study was approved by the local ethics committee.

Surgical technique

Subtotal pancreatectomy using the technique of Gall *et al.*[14] was used. All pancreatic tissue was resected except part of the tail corresponding to 5 cm of the duct and representing 10–15 per cent of the pancreatic tissue. The duct was occluded with an injection of tissue glue (Ethibloc; Ethicon, Norderstedt, Germany) and ligated to cause atrophy of the exocrine tissue. The surgical procedure included duodenectomy, cholecystectomy, and resection of the distal part of the bile duct and distal half of the stomach. Hepaticojejunostomy and gastrojejunostomy were carried out.

Diabetic history and oral glucose tolerance test

In patients known to be diabetic before surgery the history was carefully recorded. Oral glucose tolerance tests were performed in patients with no clinically evident diabetes. After an overnight fast, the patients drank 500 ml of a solution containing 75 g glucose in not more than 5 min. Plasma glucose was determined before and 2 h after the oral load; World Health Organization diagnostic criteria were used to evaluate the results[15].

Hyperglycaemic glucose clamp and glucagon stimulation

Patients arrived in the laboratory in the morning about 12 h after any previous oral intake. During this period they had been given a standardized intravenous infusion of glucose at a rate of $30 \text{ mg kg}^{-1} \text{ h}^{-1}$. For patients with insulin-dependent diabetes, insulin was added to the infusion in an amount sufficient to control the blood glucose level at between 5 and 6 mmol l^{-1}. The insulin infusion was continued at the same rate throughout the entire clamp procedure in these patients.

Short plastic cannulas were inserted into the radial artery of one arm for blood sampling and into an antecubital vein of the opposite arm for infusion. The arterial cannula was flushed with 0·9 per cent saline containing heparin 10 units ml^{-1}. In all, fewer than 1000 units heparin was given.

Basal plasma glucose and hormone levels were determined from two sets of samples taken at 5-min intervals, and then the hyperglycaemic clamp was started. The glucose infusion (200 mg l^{-1}) was given at a rate calculated to raise the plasma glucose concentration to 8 mmol l^{-1} in all patients. For priming and maintenance dose, the protocol described by DeFronzo *et al.*[16] was followed. Plasma glucose

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Table 1 *Patient characteristics before and 3 months after subtotal pancreatectomy*

Patient no.	Sex	Age (years)	Height (cm)	Weight (kg)		Serum bilirubin level (mmol l^{-1})		Fasting blood glucose level (mmol l^{-1})		Diabetes on oral glucose tolerance test		Insulin dose (units)	
				Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
1	M	39	166	62	59	135	11	17·3	5·2*	Present	Present	37	20
2	M	69	181	78	74	104	19	6·9	4·5	Present	Absent	—	—
3	F	49	171	54	49	6	11	4·0	4·3	Absent	Absent	—	—
4	F	68	160	78	69	350	13	11·3	6·6	Present	Present	42	—
5	F	73	162	81	75	407	12	20·1	6·1*	Present	Present	60	15
6	F	69	179	78	72	284	16	6·9	4·7	Present	Absent	—	—
7	F	70	160	49	45	47	10	6·0	6·2	Present	Present	28	—

*Receiving ongoing insulin treatment

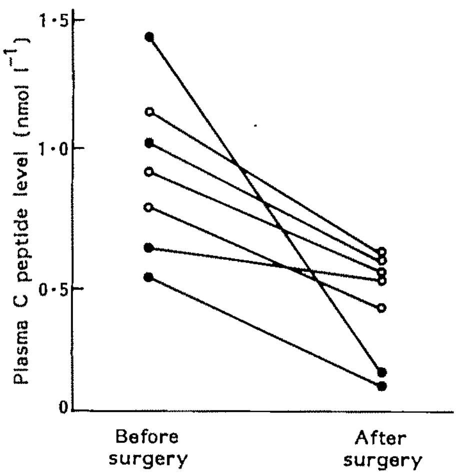

Figure 1 *Fasting plasma concentration of C peptide before and 3 months after subtotal pancreatectomy.* ●, *Diabetics;* ○, *non-diabetics*

was determined every 5 min. The maintenance dose was varied to obtain serum glucose levels of 8 mmol l^{-1}; this amount represents the glucose metabolic capacity. Samples for measurement of levels of serum insulin and C peptide were withdrawn every 10 min during the steady state. The whole-body insulin sensitivity was calculated as the amount of glucose metabolized per unit of serum insulin during the steady state, according to the method of DeFronzo *et al.*[16]. After 60 min of steady state, 1 mg glucagon was given intravenously as an additional stimulation of insulin secretion. Samples were withdrawn 1 and 6 min later for determination of plasma insulin and C peptide concentrations.

Serum glucose and hormone analyses

Plasma glucose concentration was measured using the glucose oxidase method (Beckman Glucose Analyser 2; Beckman Instruments, Brea, California, USA). Serum insulin was analysed by commercially available kits (Phadeseph insulin radioimmunoassay; Pharmacia, Uppsala, Sweden) based on solid-phase double-antibody precipitation. The C peptide level was measured as described previously[17].

Statistical analysis

Results are presented as individual data or as mean(s.e.m.). Statistical significance was tested using unpaired and paired Student's *t* tests.

Results

Six patients were diabetic before surgery: four required insulin and two were non-insulin dependent. Diabetes had been diagnosed less than 6 months before the diagnosis of cancer. After operation, the diabetic status improved in all patients. There was no evidence of diabetes in the two non-insulin-dependent diabetics, and in two of the other diabetic patients insulin treatment was unnecessary after surgery. In the remaining two diabetics, the postoperative insulin dose was more than halved (*Table 1*).

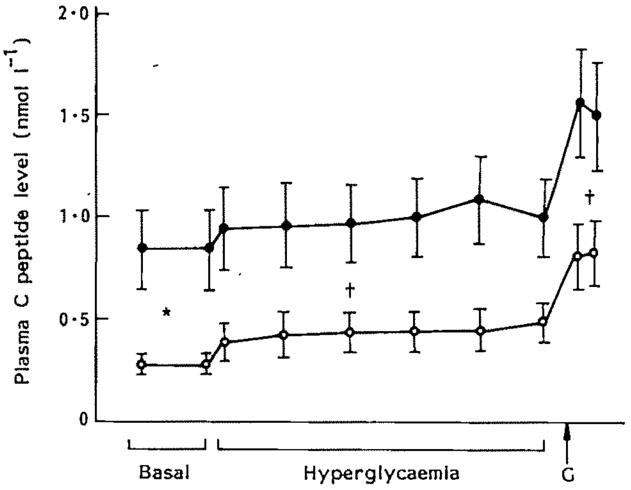

Figure 2 *Mean(s.e.m.) plasma concentration of C peptide during glucose clamp and after glucagon stimulation before* (●) *and 3 months after* (○) *subtotal pancreatectomy. G, glucagon injection. Differences between patients were significant before and after surgery in the basal state, during hyperglycaemia (calculated as the area under the curve) and after glucagon injection* (*$P < 0.05$; †$P < 0.01$, *Student's* t *test)*

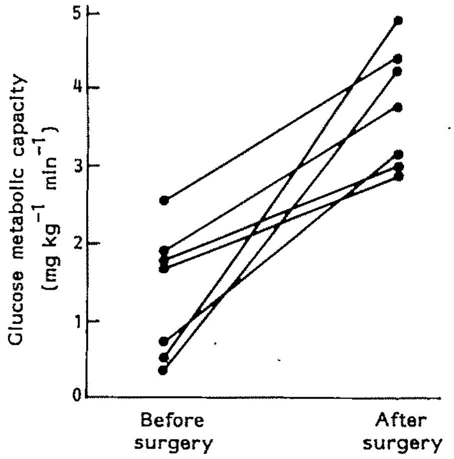

Figure 3 *Glucose metabolic capacity before and 3 months after subtotal pancreatectomy*

Fasting glucose concentrations are given in *Table 1*. Glucose levels at the initiation of the hyperglycaemic state were not significantly different at the preoperative and postoperative investigations (data not shown).

All patients had endogenous insulin production after operation. A significant reduction in the secretion, reflected as

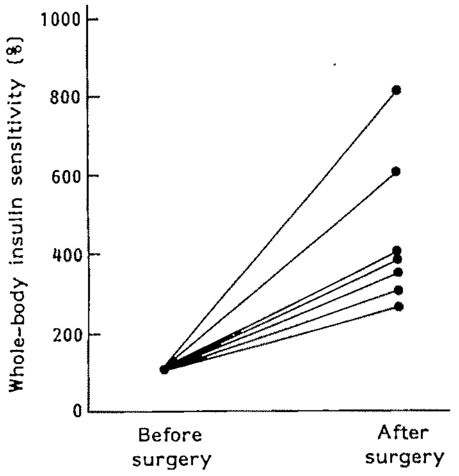

Figure 4 *Whole-body insulin sensitivity before and 3 months after subtotal pancreatectomy expressed as a percentage of the preoperative value*

the C peptide level, was observed in all patients in the fasting state ($P = 0{\cdot}02$) (*Figure 1*), during hyperglycaemia ($P = 0{\cdot}002$) and after glucagon stimulation ($P = 0{\cdot}009$) (*Figure 2*). Insulin-dependent patients had impaired C peptide production compared with non-insulin-dependent patients after, but not before, surgery (*Figure 1*).

The glucose metabolic capacity was improved in all patients after operation compared with the preoperative value ($P = 0{\cdot}007$) (*Figure 3*), as was whole-body insulin sensitivity ($P < 0{\cdot}001$) (*Figure 4*).

Discussion

Diabetic status, glucose tolerance and glucose metabolic capacity during the hyperglycaemic clamp improved in all patients after surgery, demonstrating improved glucose metabolism after removal of the pancreatic tumour. This does not support the hypothesis that impaired glucose metabolism is caused by a reduction in endocrine tissue resulting from destruction by the tumour[9]. If endocrine tissue mass were the critical factor, subtotal pancreatectomy should increase the severity of diabetes and glucose metabolism impairment. The postoperative improvement of glucose metabolism and the higher whole-body insulin sensitivity after surgery despite a marked decrease in insulin secretion suggest an increased sensitivity to insulin in the liver and/or peripheral tissues after tumour removal.

Previous results have indicated decreased insulin sensitivity in patients with pancreatic cancer[4,5,12,13], and this in the present study is demonstrated by the change in the C peptide levels in the fasting state and after glucagon stimulation in the patients who required insulin. Before surgery, C peptide levels in the present patients were above the limit suggested to determine the need for insulin[18]. This demonstrated that endogenous insulin production in these patients should normally be sufficient to avoid the need for insulin treatment and that preoperative diabetes was unlikely to have been primarily the result of insufficient insulin production. The data indicate an impaired action of insulin in patients with pancreatic cancer and suggest that this abnormality was corrected after surgical removal of the tumour.

Impaired glucose tolerance has been reported in up to 30 per cent of patients with different types of tumour[19]. The frequency of diabetes and glucose intolerance is higher in those with pancreatic cancer[19]. The severity of the disorder is greater and nearly half are frankly diabetic. Glucose intolerance occurs more frequently in cachectic patients with advanced tumours[20], but in the present study the tumours were small and there were no metastases.

Other conditions, such as rapid weight loss and jaundice, may cause impaired glucose metabolism and are frequently associated with pancreatic cancer[21,22]. Six of the seven present patients had raised plasma bilirubin levels and all had a history of weight loss before surgery. Diabetes may occur in both jaundiced and non-jaundiced patients with pancreatic cancer[5]; additional weight loss, as a result of a postoperative adaptation, occurred in all patients between surgery and the postoperative investigation. It is unlikely that the dramatic overall improvement in glucose metabolism seen after surgery in the present patients can be explained by these factors. Postoperative weight loss occurred mainly during the period immediately after surgery, and at the time of the postoperative investigation no major weight loss was seen for any patient.

Data from this study suggest that pancreatic tumours produce a factor that has a negative influence on the metabolism of glucose, by a direct action on extrapancreatic tissue or by indirect effects on other pancreatic cells.

Pancreatic tumours other than adenocarcinoma are characterized by extensive production of different peptides and hormones causing a variety of clinical syndromes such as diabetes[23]. A large number of endocrine cells are found in up to 80 per cent of exocrine pancreatic adenocarcinomas[24,25]. Amine and peptide production may not be restricted to endocrine pancreatic tumours but may also be an effect of exocrine pancreatic adenocarcinoma. Glucagon, somatostatin and islet amyloid polypeptide, for example, have a negative influence on glucose tolerance and reduce insulin sensitivity[26–28].

Pancreatic adenocarcinoma may produce a diabetogenic peptide that is responsible for the disturbances observed in glucose metabolism and other metabolic processes. Further studies are required to confirm this hypothesis and to isolate the factor involved. Identification of such a peptide could be of major importance in the early diagnosis of pancreatic cancer and provide important information on the pathogenetic mechanism of other types of late-onset diabetes.

Extensive surgery in patients with pancreatic cancer can improve long-term survival[29], and more radical operative procedures have been adopted in surgical treatment of this disease. The present study shows that preservation of some pancreatic tissue is of clinical importance because it may prevent the development of postoperative diabetes. Tissue preservation is likely to benefit patients who are diabetic before surgery, because diabetes may improve or disappear after tumour excision.

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Surgical workshop

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Thoracoscopic pancreatic denervation for pain control in irresectable pancreatic cancer

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Pancreatic cancer is the fourth most common cause of death from malignancy in the USA. Pain is the most frequent and distressing feature of this disease, and most patients are suitable for palliation only. Relief of pain is usually obtained through the use of narcotic analgesics. Pain fibres can also be interrupted at the coeliac plexus by injection of bupivacaine, alcohol or phenol, or by splanchnicectomy at laparotomy or thoracotomy[1,2].

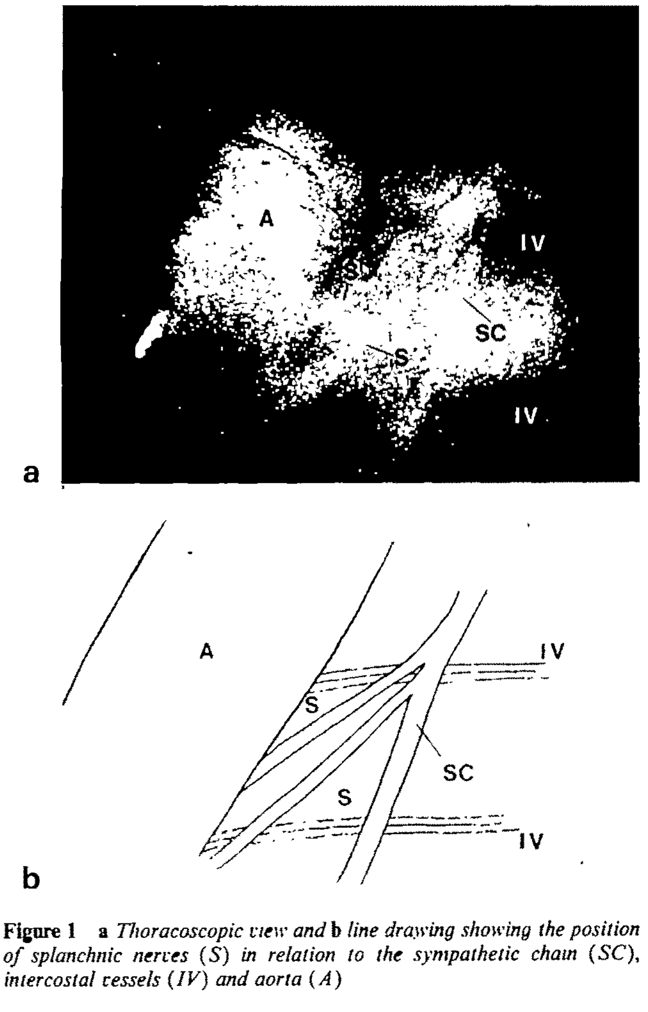

Figure 1 **a** *Thoracoscopic view and* **b** *line drawing showing the position of splanchnic nerves (S) in relation to the sympathetic chain (SC), intercostal vessels (IV) and aorta (A)*

A technique of splanchnicectomy and truncal vagotomy via a left thoracotomy in alcoholic pancreatitis has been described with encouraging resultant pain relief[1]. Thoracoscopic denervation of the pancreas has not previously been reported.

Surgical technique

A 60-year-old man presented with epigastric pain. Abdominal computed tomography and arteriography showed a large pancreatic mass involving the neck and body of the gland and invading the coeliac axis. Percutaneous biopsy demonstrated adenocarcinoma. At the time of referral the patient was taking large amounts of morphine, but pain disturbed his sleep and led to anorexia with an 8-kg weight loss. Sedation and constipation were additional problems. Thus pancreatic denervation was indicated.

With the patient in the right lateral position, general anaesthesia was established with double-lumen endotracheal intubation and single-lung (right) ventilation. Disposable 11-mm thoracoscopic cannulas (US Surgical, Norwalk, Connecticut, USA) were introduced through the fourth and sixth intercostal spaces in the anterior axillary line and through the seventh and ninth spaces in the posterior axillary line of the left chest. A 10-mm operating thoracoscope (Karl Storz Endoscopes, Culver City, California, USA) was then introduced[3]. The sympathetic chain was readily identified coursing over the ribs 2 cm posterior and lateral to the aorta (*Figure 1*). The greater splanchnic nerve (T5–T9) and lesser splanchnic nerve (T10–T11) were identified, and the parietal pleura was incised. Each nerve was clipped and electrocoagulated. Additionally, the anterior and posterior vagal trunks were identified and divided[4]. A single chest tube was placed. The operating time was 80 min.

The patient awoke free from pain, had the chest tube removed on day 2 and was discharged a day later. He remained free from epigastric pain at follow-up after 1 month.

Discussion

Pancreatic nociceptive fibres reach the sympathetic chain via the coeliac plexus, the paired coeliac ganglia and the greater

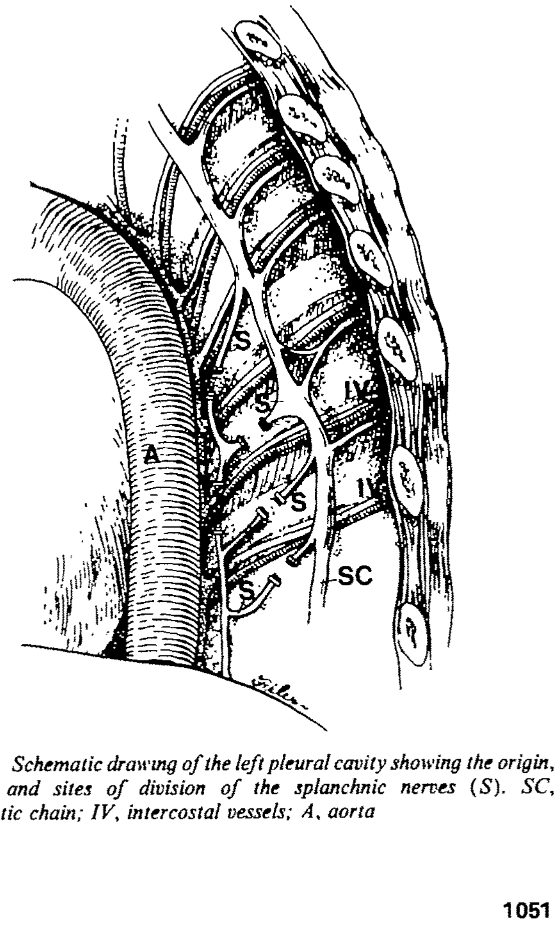

Figure 2 *Schematic drawing of the left pleural cavity showing the origin, relations and sites of division of the splanchnic nerves (S). SC, sympathetic chain; IV, intercostal vessels; A, aorta*

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and lesser splanchnic nerves. Interruption of these fibres at the coeliac plexus may be performed by precise percutaneous injection of alcohol or phenol. Complications of this technique are related to the proximity of neural and vascular structures.

Interruption of the greater and lesser splanchnic nerves can be undertaken as an open surgical procedure[2]. At thoracoscopy the splanchnic nerves are readily found and divided by identification of the sympathetic chain, which is visible through the parietal pleura (*Figures 1* and *2*). The addition of vagotomy may be of further benefit by reducing acid stimulation of pancreatic secretion[5].

The thoracoscopic route for splanchnicectomy confers a low morbidity rate and provides better visibility of neural structures[3]. The right side can be similarly approached in the minority of patients with persistent pain in the right upper quadrant. This is a minimally invasive video-assisted approach to a difficult management problem; it may find application in other upper abdominal pain syndromes.

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The authors thank Ron Filer for drawing *Figure 2*.

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Case report

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Late discharge of stones after laparoscopic cholecystectomy

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Stones that fall out of the gallbladder during laparoscopic cholecystectomy may be difficult to retrieve. Although this mishap may have no untoward sequelae, a patient is presented who developed recurrent intermittent sepsis associated with the discharge of dropped stones through one of the laparoscopic cannula sites.

Case report

A 77-year-old woman with known gallstones was admitted with an acute episode judged to be caused by empyema of the gallbladder. Initial treatment was by percutaneous drainage and administration of intravenous antibiotics. Some 6 weeks later the woman underwent laparoscopic cholecystectomy. Preoperative endosonography showed a normal common bile duct 4·7 mm in diameter, and results of liver function tests were normal.

Four cannulas were used: one umbilical and one epigastric (each of 10 mm), and two right-sided of 5 mm for retraction of the gallbladder. Prophylactic antibiotics were given. The omentum, gallbladder and liver were densely adherent to each other and a difficult cholecystectomy ensued during which the gallbladder was entered and some stones spilled into the peritoneal cavity. As many stones as possible, but not all, were retrieved. The gallbladder was removed through the incision made for the umbilical cannula. The patient made an uncomplicated recovery and was discharged on the third day after surgery.

After 5 months she returned with an 8-week history of a tender swelling in the epigastrium. Examination revealed erythema and tenderness around the scar of the epigastric port. This area was explored under anaesthesia; a sterile abscess was found with a 2 × 1 × 1 mm gallstone at its centre. Histological examination of the track showed a foreign body reaction with cholesterol clefts and bile-stained material in giant cells.

The pain and swelling settled, only to recur with the spontaneous discharge of a stone from the same site some months later followed by resolution of the problem.

Discussion

Laparoscopic cholecystectomy has proved to be a popular operation with surgeons and patients, and has become the accepted way of removing the gallbladder. During difficult operations the gallbladder may be inadvertently entered and stones spilled into the peritoneal cavity. Since it is not always possible to retrieve all the stones, either some must be left in the abdomen or the operation must be converted to an open procedure to remove them. Experience has been that stones left in the abdomen usually give no trouble, with the exception of the present case.

Tumour arising in the gallbladder can be implanted at the exit port of the gallbladder through the abdominal wall[1,2], but in the present case the stones migrated through the site of the epigastric rather than the umbilical cannula.

Once gallbladder puncture has occurred and stones are lost then some are usually irretrievable, but it may be better to extract all the remaining stones into a bag before proceeding so as to reduce the loss of stones to a minimum.

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Complete common bile duct division at laparoscopic cholecystectomy: management by percutaneous drainage and endoscopic stenting

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Endoscopic treatment of common duct injury, stricture and fistula is a safe and effective form of therapy[1] and has been employed after laparoscopic cholecystectomy for leakage from the cystic duct[2] and stricture of the common bile duct (CBD)[3]. In a case of complete division of the CBD after laparoscopic cholecystectomy complicated by biliary ascites, successful early management is reported by percutaneous peritoneal catheter drainage and endoscopic stenting.

Case report

A 53-year-old obese hypertensive woman underwent laparoscopic cholecystectomy for symptomatic gallstones. The operative report included application of clips and division across two duct structures, followed by significant bleeding on removal of the gallbladder; this was controlled with diathermy. After operation the patient had an episode of chest pain, and became jaundiced on day 5. Endoscopic retrograde cholangiography (ERC) showed complete obstruction where the clips had been applied across the CBD (*Figure 1a*). The patient was transferred to the authors' unit, where electrocardiography and cardiac enzyme levels suggested a recent inferior myocardial infarction. Surgical repair of the bile duct injury was thus deferred and the patient managed expectantly without external biliary drainage.

At 3 weeks after laparoscopic cholecystectomy the patient developed tense biliary ascites, which was drained percutaneously using an 8-Fr pigtail catheter (Meditech, Boston Scientific, Massachusetts, USA) under ultrasonographic guidance. Some 5 litres of bile was drained, followed by a daily output of 500 ml. The patient was reassessed endoscopically, sphincterotomy was performed and a coaxial catheter (Cotton–Huibregtse stent set (CHBS–10-9); Wilson Cook Medical, Winston Salem, North Carolina, USA) with guidewire was pushed through the obstruction, dislodging the clip. With careful manipulation of the guidewire, the catheter was advanced across the defect into the intrahepatic ducts (*Figure 1b*). A 10-Fr stent was placed across the site of the leak into the right hepatic system. The percutaneous drainage catheter was removed after 4 days and another placed 4 weeks later into an infected subphrenic collection. A second stent was placed alongside the first, to improve biliary drainage.

ERC 6 months after stenting revealed no leak from the site of the duct injury (*Figure 2a*). Both stents were removed and there was no evidence of stricture (*Figure 2b* and *c*). Findings on serum biochemistry 6 months after removal of the endoprostheses were normal.

Discussion

Although the reported incidence of CBD injury after laparoscopic cholecystectomy ranges from 0·3 to 0·5 per cent[4], the true incidence is probably higher. Injury usually occurs during the early experience of the operator. The risk of injury increases if there is difficulty in identifying the bile duct anatomy, and recognition of injury may be delayed[5].

The present patient posed an unusual problem in that there was a prohibitive risk for conventional surgical repair, because of a recent myocardial infarction, and late presentation with biliary ascites 3 weeks after injury. The delayed bile leak probably resulted from either dislodgement of the proximal clip or ischaemic necrosis of the bile duct at the point of clip application. The value of catheter drainage of biliary ascites[6] was clear: this approach avoided surgery and allowed internal biliary drainage to be performed as an elective procedure. The ease with which the clip was dislodged by the coaxial catheter was surprising, although clips applied in error during

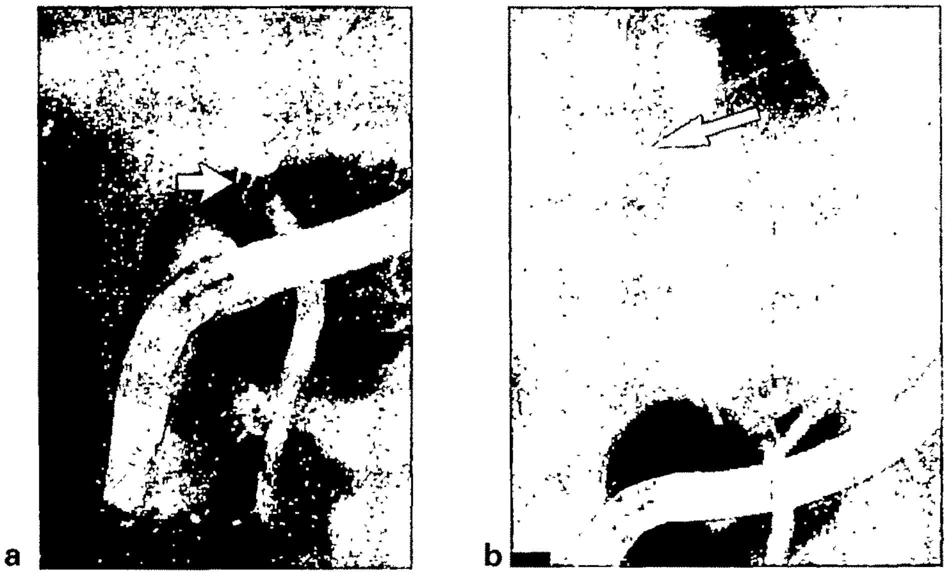

Figure 1 *Endoscopic retrograde cholangiograms showing* **a** *obstruction at the level of the clips (arrow) and* **b** *the coaxial catheter (arrow) manipulated into the intrahepatic biliary system*

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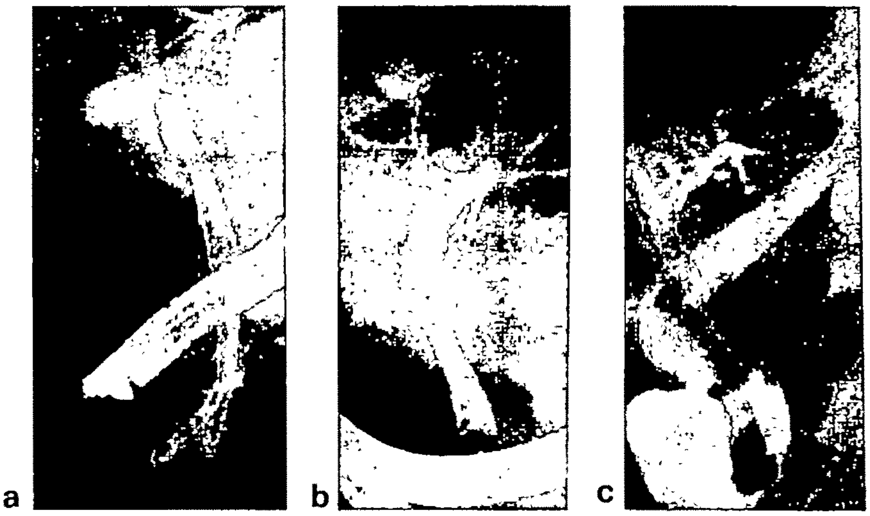

Figure 2 **a** *Contrast injection past stents showing no leak;* **b** *balloon-assisted injection to assess stricture;* **c** *completion view to assess emptying of the biliary system*

laparoscopic surgery are easily removed. Successful cannulation of the proximal bile ducts suggested proximity of the divided ends without retraction of the proximal duct, or that the bile duct was simply clipped and not divided as was reported by the surgeon.

Although surgical repair of bile duct injury is the standard treatment, the efficacy of non-operative stenting of bile duct fistula and stricture in the short to medium term has been demonstrated[1]. The endoscopic route offers advantages over the percutaneous transhepatic approach in that it can be performed in the presence of ascites, is feasible in the absence of intrahepatic duct dilatation, and offers easier access for replacement of the stents. The early absence of stricture after removal of the stents is encouraging in the patient presented, but careful long-term observation will be required. This case illustrates the value of interventional radiological and endoscopic procedures in the early management of bile duct injury.

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Effect of antitumour necrosis factor treatment on circulating tumour necrosis factor levels and mortality after surgery in jaundiced mice

Tumour necrosis factor (TNF) may play an important role in the increased incidence of complications after surgery in patients with obstructive jaundice. This study evaluated the effect of three different anti-TNF treatments, a monoclonal anti-TNF antibody (TN3), pentoxifylline and lactulose, on outcome after severe surgical trauma in mice with experimental biliary obstruction. Circulating serum TNF levels and mortality rate were monitored. Severe surgical trauma, such as renal ischaemia, in jaundiced mice resulted in increased levels of circulating TNF (3·5 ng/ml) and a high mortality rate (54 per cent). The three different anti-TNF treatments caused a significant reduction in postoperative levels of circulating TNF (TN3, $P < 0·001$; pentoxifylline, $P < 0·01$; lactulose, $P < 0·05$). Treatment with TN3 and pentoxifylline did not lead to a significantly reduced mortality rate (36 and 44 per cent respectively). Only lactulose treatment produced a significantly reduced mortality rate (7 per cent, $P < 0·01$). TNF is therefore not the only mediator responsible for death after surgery in jaundiced mice. Other mechanisms affected by lactulose are also involved.

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Surgery in patients with obstructive jaundice is associated with a significant morbidity rate and a high incidence of infectious complications[1–3]. Several underlying mechanisms, related to high levels of serum bilirubin and bile acid[4], depressed immune function[5–9], poor nutritional status[10,11] and endotoxaemia[2,12–15], may play a part in this phenomenon. Internal and external biliary drainage, and administration of bile acid, mannitol and oral lactulose have been studied for the possible prevention of these complications but without substantial benefit[7,15–24].

Endotoxaemia in humans and animals with biliary obstruction correlates with the occurrence of postoperative complications[14,20,25]. It results in circulating tumour necrosis factor (TNF), a central mediator of endotoxin toxicity[26]. Circulating TNF can be detected in mice with experimental biliary obstruction and may play a role in the pathogenesis of the complications seen after surgery[27].

This study compared the effects of different treatments that interfere with either the effects of TNF or the release of TNF in mice with biliary obstruction, using bilateral renal ischaemia as a severe surgical trauma. The effects on circulating TNF and mortality rate were studied. The anti-TNF agents used were a monoclonal anti-TNF antibody (TN3), pentoxifylline, which is known to inhibit TNF release *in vitro* and *in vivo* without affecting interleukin 6 release[28,29], and oral lactulose, which has been shown to reduce lipopolysaccharide-induced TNF production *in vitro*[30].

Materials and methods

Animals

Female Swiss mice weighing 27·5–34·5 g (Charles River Breeding Laboratories, Heidelberg, Germany) were maintained on a standard laboratory diet and allowed free access to water.

Reagents

Bovine serum albumin, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, *N,N*-dimethylformamide and substrate *o*-phenyldiamine were obtained from Sigma Chemicals (St Louis, Missouri, USA). TN3, a hamster monoclonal antibody specific for murine TNF[31], was a gift from Drs K. C. F. Sheehan and R. D. Schreiber, St Louis, Missouri, USA and produced by Celltech, Slough, UK. Sodium dodecyl sulphate was obtained from Bio-Rad (Richmond, California, USA). Peroxidase-conjugated goat antirabbit immunoglobulin (Ig) G was obtained from Jackson (Westgrove, Pennsylvania, USA). Polyclonal rabbit antimurine TNF serum was produced by injecting rabbits with murine TNF provided by Knoll/BASF (Ludwigshafen, Germany). Pentoxifylline was donated by Hoechst (Wiesbaden, Germany). Lactulose (Duphalac) was given by Duphar (Weesp, The Netherlands).

Surgical procedures

Mice were operated on under light ether anaesthesia on a temperature-controlled water mattress. Through a 1·0-cm mid-abdominal incision, the common bile duct was ligated and divided as a modification[27] of the method of Pinto and Kaplun[6]. After surgery all mice received 1 ml saline subcutaneously.

Renal ischaemia was produced 18 days after bile duct ligation (BDL). Mice were anaesthetized with ether, and the renal vascular pedicles were clamped for 30 min with soft-tip clamps to cause renal ischaemia. During the ischaemia period, the abdomen was closed, ether anaesthesia interrupted and the animals allowed to recover. In sham-operated mice, the renal vessels were dissected but not clamped. After 30 min of (sham) ischaemia, the abdomen was opened again (also in the sham group) and clamps were removed (or 'sham' removed). After macroscopic confirmation of reperfusion, the abdomen was closed. Blood was obtained by puncture of the retrobulbar venous plexus.

Experimental design

After BDL, mice were randomly divided into five experimental groups (*Table 1*). Renal ischaemia was produced at day 18. Group 1 received sham renal ischaemia. Group 2 received renal ischaemia without pretreatment. Group 3 received anti-TNF antibody (TN3), 0·5 mg per mouse before induction of renal ischaemia. Group 4 received

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Table 1 *Experimental design*

Time (days)	Group 1 ($n = 10$)	Group 2 ($n = 13$)	Group 3 ($n = 11$)	Group 4 ($n = 9$)	Group 5 ($n = 14$)
0	BDL	BDL	BDL	BDL	BDL
15	—	—	—	—	Lactulose
16	—	—	—	—	Lactulose
17	—	—	—	—	Lactulose
18	Sham renal ischaemia	Renal ischaemia	TN3–renal ischaemia	Pentoxifylline–renal ischaemia	Lactulose–renal ischaemia

BDL, bile duct ligation; TN3, monoclonal antibody against tumour necrosis factor (TNF). Serum TNF was measured by enzyme-linked immunosorbent assay 90 min after reperfusion. Survival was assessed over 120 h

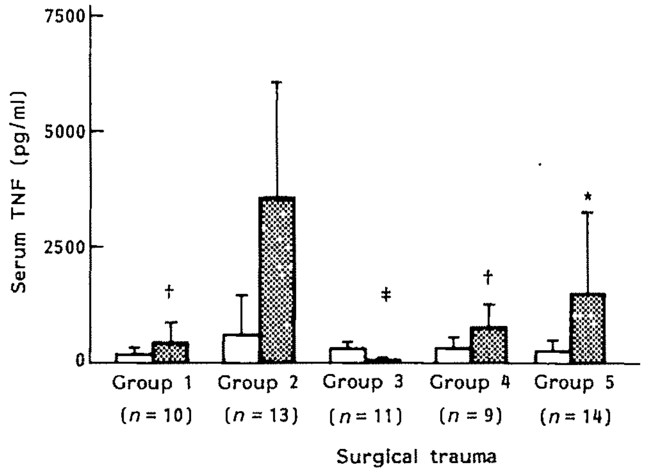

Figure 1 *Serum tumour necrosis factor (TNF) levels after renal ischaemia in mice with bile duct ligation (BDL).* □, *TNF levels at day 17 after BDL, 1 day before the surgical trauma;* ▨, *TNF levels 90 min after surgical trauma. Values are mean(s.d.).* *$P < 0{\cdot}05$; †$P < 0{\cdot}01$; ‡$P < 0{\cdot}001$ versus *group 2 (ANOVA)*

pentoxifylline before operation 1 mg per mouse and group 5 received oral lactulose before induction of renal ischaemia. TN3 was given intraperitoneally 4 h before induction of ischaemia. Group 4 received pentoxifylline at $t = -2$ h intraperitoneally. Group 5 was treated for 3 days with oral lactulose (0·25 ml 30 per cent Duphalac syrup in water) twice daily before induction of renal ischaemia. Blood was sampled 1 day before induction of ischaemia and 1·5 h after recovery from ischaemia (time of TNF peak; unpublished data). After blood collection, all mice received 1 ml saline subcutaneously.

Previous experiments have shown that after 18 days mice have substantial plasma levels of bilirubin[27]. Bilirubin concentrations were measured in randomly selected blood samples of 27 mice taken 1 day before induction of ischaemia to ensure biliary obstruction (mean(s.d.) 349(31) μmol/l). Mice with bile leakage or which did not survive 1·5 h after renal ischaemia were excluded. This led to an unequal distribution of animals over the different groups. Survival was monitored for 5 days after renal ischaemia (day 23) in a so-called 'steady state' obstructive jaundice to prevent interference of mortality of end-stage biliary obstruction (occurring 25 days after biliary obstruction).

Enzyme-linked immunosorbent assay for murine tumour necrosis factor

TNF assay was performed as described by Dentener *et al.*[32]. The assay had a lower detection limit of 50 pg/ml TNF.

Statistical analysis

Differences in serum TNF levels were calculated using analysis of variance (ANOVA)[33]. Significance levels for differences in mortality rate between treatment groups were determined by the log rank test. $P < 0{\cdot}05$ was considered significant.

Results

Serum tumour necrosis factor levels before and after renal ischaemia in mice with bile duct ligation

Preoperative blood samples, collected 1 day before renal ischaemia, 17 days after BDL, showed that significant levels of TNF were circulating in the majority of mice, with a mean TNF level of approximately 250 pg/ml (*Figure 1*). There were no significant differences in TNF levels before surgery in the five experimental groups. Surgical trauma in mice with BDL resulted in a sharp increase in circulating TNF concentration, with mean levels of serum TNF of 3·5 ng/ml 1·5 h after operation (*Figure 1*). This was significantly different ($P < 0{\cdot}01$) from the value in sham-operated mice, which showed only a minor increase in levels of circulating TNF. All anti-TNF treatments significantly reduced postoperative levels of TNF. TN3 was the most potent inhibitor. Pentoxifylline negated the increase in circulating TNF level, resulting in concentrations ranging from 180 to 1790 pg/ml. Lactulose was less potent in inhibiting the increase in serum TNF level after operation, leading to concentrations ranging from 160 to 5600 pg/ml.

Table 2 *Mortality after bilateral renal ischaemia in mice with bile duct ligation*

	Mortality rate (%)	P*
Group 1	0	<0·01
Group 2	54	—
Group 3	36	0·48
Group 4	44	0·79
Group 5	7	<0·01

Survival was assessed over 120 h. **Versus* group 2 (log rank test)

Mortality after surgical trauma in mice with bile duct ligation

Bilateral renal ischaemia resulted in a mortality rate of 54 per cent in group 2 (*Table 2*). No deaths were observed after sham operation ($P < 0{\cdot}01$). Despite the fact that pretreatment with TN3 resulted in significantly reduced TNF levels, this did not lead to a significantly lower mortality rate (36 per cent, $P = 0{\cdot}48$). Pretreatment with pentoxifylline was also not effective in reducing the mortality rate (44 per cent, $P = 0{\cdot}79$), but pretreatment with lactulose resulted in a significantly lower mortality rate (7 per cent, $P < 0{\cdot}01$ *versus* the non-treated group).

Discussion

TNF is known to play a pathogenic role in septic shock, transplant rejection and gastrointestinal diseases[34–39], and serum TNF levels correlate with a fatal outcome in patients with sepsis[34,35]. The work of Tracey *et al.*[40] indicates that inhibition of TNF production by anti-TNF antibodies can prevent such endotoxin-induced mortality in animals. In contrast with these data, endogenous TNF is involved in the immune process responsible for recovery from experimental peritonitis, indicating important physiological functions for this polypeptide[41]. TNF may have a role in the pathogenesis of the complications seen after surgery in jaundiced patients[20]. Recently it was shown that mice undergoing experimental BDL develop circulating levels of TNF[27].

In the present study, renal ischaemia in jaundiced mice produced a high mortality rate (54 per cent) and increased levels of circulating TNF. As TNF may have a central role in the observed mortality, the effects of different anti-TNF treatments were investigated. Whereas TN3 and pentoxifylline are specific anti-TNF agents, lactulose, as well as reducing endotoxin-induced TNF production by monocytes[20,30], has other effects attributable to its antiendotoxin properties[17,42]. Anti-TNF treatment led to a significant reduction in postoperative levels of circulating TNF. Although TN3 was the most potent inhibitor, it did not lead to a significantly reduced mortality rate (36 per cent). The same was observed with pentoxifylline treatment, which resulted in a mortality rate of 44 per cent. The failure of TN3 and pentoxifylline treatment is probably not due to bacteraemia, since several reports have described the presence of systemic endotoxaemia without bacteraemia in the presence of severe hepatic damage[43,44]. Katz *et al.*[45] showed that BDL did not affect bacterial clearance from the circulation. In the present study, only lactulose treatment resulted in a significantly reduced mortality rate (7 per cent), although it was less effective at reducing circulating levels of TNF. The beneficial effect of lactulose on mortality rate after surgery in mice with BDL agrees with previous reports, which have shown that lactulose prevents endotoxin-related complications in jaundiced patients[17] and reduces the mortality rate after surgery in jaundiced rats[20]. In some studies this effect has been attributed to lactulose inactivating endotoxin, as measured by the *Limulus* amoebocyte lysate assay[17,42]. The present group, however, did not observe this inactivation but showed that lactulose inhibits the production of TNF by monocytes in response to endotoxin[30].

The mechanism by which lactulose administration results in reduced mortality remains unclear, but it is administered orally and will be present in the intestinal lumen, which is the most important source of endotoxins[13,17,20,46]. Under normal conditions, only very limited translocation of bacteria and leakage of these endotoxins occurs[13,17,47]. In situations of mucosal damage, stress, inflammation or BDL, however, intestinal permeability is increased[2,15,17,46]. Lactulose may have a beneficial effect on leakage of these endotoxins into the circulation[17,48–50]. This is supported by reports showing that endotoxaemia is reduced by administration of lactulose[17,42].

The gut is a potential source of inflammatory products; in patients with active ulcerative colitis, large amounts of TNF were observed in the faeces whereas very little TNF was present in the circulation[37,51]. If endotoxins and cytokines produced in the bowel are important in the observed mortality, then lactulose may exert a preferential function in the gut.

In summary, renal ischaemia in mice with biliary obstruction is associated with high levels of circulating TNF and a high mortality rate. Of the anti-TNF treatments used, only lactulose administration resulted in a reduced mortality rate with a reduction in circulating TNF levels. Circulating TNF is therefore not the ultimate factor in the mortality observed in these mice, and further studies are needed to confirm the presence of cytokines in jaundiced patients and to elucidate the pathophysiology of mortality after surgery.

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Probability of rejection predicted from ultrasonographic measurement of renal transplant swelling

Serial ultrasonographic measurements of renal transplant cross-sectional area were used to quantify allograft swelling as a diagnostic test of acute rejection. Eighty consecutive episodes of acute allograft dysfunction (rise in creatinine level $\geqslant 10$ *per cent or* $\geqslant 30\ \mu\mathrm{mol\,l^{-1}}$*) were investigated. Needle core biopsy was performed in all cases to diagnose acute rejection. Rejecting transplants demonstrated a median (interquartile range) swelling of 16·2 (12·1–25·5) per cent compared with 2·2 (−2·0 to 8·4) per cent for non-rejecting organs* ($\mathrm{P} < 0{\cdot}001$)*. A* $\geqslant 10$ *per cent increase as the diagnostic threshold for rejection yielded a sensitivity of 80 per cent, specificity of 77 per cent, positive predictive value of 85 per cent, negative predictive value of 71 per cent and overall accuracy of 79 per cent. Using a logistic regression model, predictive probabilities of rejection for individual changes in cross-sectional area were calculated. A 20 per cent increase was associated with a predicted probability of rejection of 87 per cent (95 per cent confidence interval 75–94 per cent). There was a significant correlation between the functional severity of rejection and the degree of transplant swelling* ($r_S = 0{\cdot}63$, $\mathrm{P} < 0{\cdot}001$)*. Ultrasonographic measurement of renal transplant cross-sectional area is a simple non-invasive test for the diagnosis of acute rejection.*

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Acute rejection of renal allografts is accompanied by mononuclear cell infiltration and interstitial oedema, which cause swelling of the rejecting kidney. Various parameters of transplant size can be accurately measured with standard ultrasonographic equipment and the cross-sectional area at the hilum has been shown to be a reliable index of renal size[1]. Serial monitoring of renal transplants by ultrasonographic measurements has been used in this centre for several years. Earlier work demonstrated that this technique was useful in distinguishing acute rejection from cyclosporin toxicity and other causes of acute allograft dysfunction[2,3]. The purpose of the present prospective analysis was to assess the predictive value of ultrasonography in the diagnosis of acute rejection.

Patients and methods

All ultrasonographic examinations were performed by the same ultrasonographer (A.B.) using an Aloka SSD-630 real-time machine (Keymed, Southend, UK) fitted with a 3·5-MHz linear-array probe. After orientation of the longitudinal and transverse axes of the kidney, the probe was lined up to demonstrate a transverse cross-section at the hilum. The largest cross-section was found by examination of the real-time image as the probe was moved up and down along the long axis of the transplant. When the appropriate section was found the frame was frozen to allow measurements to be taken. A hand-guided cursor was used to trace the outline of the hilar cross-section and from this line the machine software calculated and displayed the cross-sectional area. Four measurements of graft cross-sectional area were made each day and these values and their means recorded on a database.

Intrarenal anatomical reference points were used to identify the same cross-section of the kidney on sequential scans. The first reference point identified was either a major vessel or the ureter at the hilum and the second was usually a prominent vessel within the renal parenchyma itself. Subsequent daily identification of these reference points was facilitated by making hard copies of the cross-section under study. The use of a subcuticular suture and an Opsite dressing (Smith and Nephew, Hull, UK) allowed scanning in the early postoperative period without disturbing the wound. Some 2–3 days were allowed for wound tenderness to settle and then transplants were scanned daily until discharge from hospital after 10–14 days. Subsequent ultrasonography was performed on an outpatient basis at more variable intervals, but for all episodes of acute graft dysfunction daily scanning was reintroduced.

Acute allograft dysfunction was defined as an absolute rise in serum creatinine level of $\geqslant 30\ \mu\mathrm{mol\,l^{-1}}$ or an increase of $\geqslant 10$ per cent in serum creatinine concentration between successive estimates. The difference between measurements of allograft cross-sectional area was expressed as a percentage change according to the formula:

$$\text{Difference in area} = \frac{\text{peak area} - \text{baseline area}}{\text{baseline area}} \times 100\%$$

The baseline cross-sectional area was defined as the measurement immediately before the episode of dysfunction. Previous work has suggested that an increase of $\geqslant 10$ per cent in graft cross-sectional area represents a significant degree of transplant swelling, indicating a diagnosis of acute rejection if both urinary tract infection and ultrasonographic evidence of marked pelvicalyceal dilatation (suggesting ureteric obstruction) have been excluded[1,3].

In all cases of acute allograft dysfunction a needle core biopsy was taken under ultrasonographic control using the automated Biopty gun and needle (Bard, Crawley, UK)[4]. Histological slides prepared from biopsy material were examined by one of two consultant pathologists with an interest in renal pathology. The histopathology report was taken as the 'gold standard' for the presence or absence of acute rejection. Ultrasonographically measured changes in transplant cross-sectional area were compared with histological findings.

The severity of acute rejection was assessed both histologically and functionally. All needle core biopsies showing evidence of rejection were graded as mild, moderate or severe by subjective estimation of the density of the mononuclear cell infiltrate and the degree of tubular and vascular damage. The functional severity of rejection was quantified by estimation of the fall in creatinine clearance rate during the rejection episode. Creatinine clearance rates were derived from serum creatinine level, age, weight and sex using a verified formula[5].

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All patients underwent immunosuppression with cyclosporin A, at an initial dose of 17 mg kg^{-1} day^{-1} (reducing by 2 mg kg^{-1} week^{-1} to a baseline dose of 7 mg kg^{-1} day^{-1} at 6 weeks) in combination with prednisolone alone, at an initial dose of 10 mg kg^{-1} day^{-1} (reducing by 1 mg kg^{-1} week^{-1} to a baseline dose of 4 mg kg^{-1} day^{-1} at 6 weeks) or as part of triple therapy with prednisolone and azathioprine (1 mg kg^{-1} day^{-1}).

Statistical analysis

Changes in transplant cross-sectional area for rejecting and non-rejecting kidneys were compared using the Mann–Whitney *U* test. The accuracy of ultrasonography in the diagnosis of acute rejection was expressed as sensitivity, specificity, predictive values and overall accuracy[6]. Predictive probabilities of rejection for individual changes in transplant cross-sectional area were calculated using a logistic regression model[7] with rejection or non-rejection as the response and percentage change in transplant cross-sectional area as the regressor variable. Data were linearized using log transformation and a regression line fitted by least-squares estimation to produce cumulative probability curves for the mean and 95 per cent confidence interval (c.i.). The relationship between changes in transplant cross-sectional area and the functional severity of rejection (expressed as the fall in estimated creatinine clearance rate) was evaluated using the Spearman rank correlation test, with significance at $P < 0·05$.

Results

Eighty consecutive episodes of acute renal allograft dysfunction occurring in 58 patients over a 2-year period were studied. Ultrasonographic measurements were made between 1 and 300 days after transplantation; the vast majority were performed during the first 3 months after transplantation. A total of 49 episodes of allograft dysfunction were related to rejection and 31 to other causes (cyclosporin toxicity, acute tubular necrosis, glomerular disease, chronic rejection and a group in which the histological appearance was essentially normal). The median (interquartile range) change in transplant cross-sectional area during rejection episodes was 16·2 (12·1–25·5) per cent, which was significantly higher than in graft dysfunction unrelated to rejection (2·2 (−2·0 to 8·4) per cent) ($P < 0·001$).

Taking a rise in transplant cross-sectional area of ≥10 per cent as the diagnostic threshold for rejection, there were 39 correctly positive ultrasonograms and ten false-negative scans for rejecting kidneys. In the 31 other cases of graft dysfunction there were 24 correctly negative and seven false-positive scans (*Figure 1*). The accuracy statistics for a diagnostic threshold at 10 per cent swelling are therefore sensitivity 80 per cent, specificity 77 per cent, positive predictive value 85 per cent, negative predictive value 71 per cent and overall accuracy 79 per cent (*Table 1*).

The predicted probability of rejection in relation to changes in transplant cross-sectional area is shown in *Figure 2*. The fitted logistic model yielded the relationship $P_r = 1/(1+\exp(-1·624 + 0·175y))$, where P_r is the probability of rejection and y is the percentage change in transplant cross-sectional area. From this the mean (95 per cent c.i.) probabilities of rejection were calculated for a number of different changes in transplant cross-sectional area (*Table 2*).

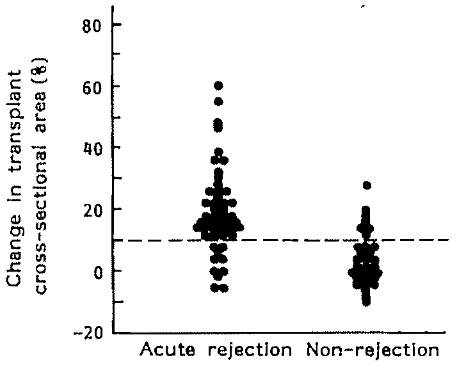

Figure 1 *Change in ultrasonographically measured transplant size during episodes of dysfunction related to rejection and other causes*

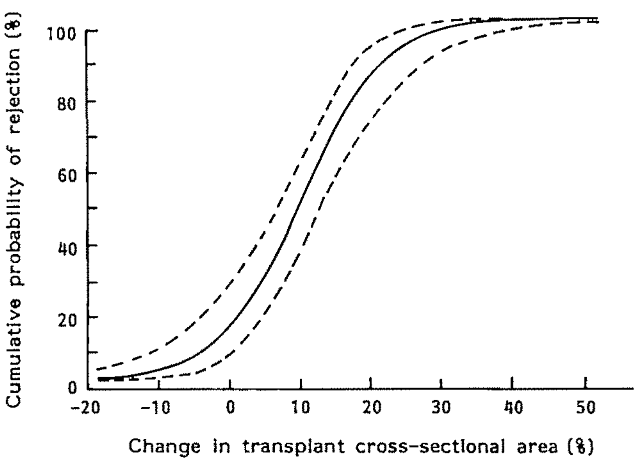

Figure 2 *Predicted probability of rejection in relation to ultrasonographically measured change in transplant size.* ——, *Mean;* – – –, *95 per cent confidence interval*

Table 1 *Accuracy of ultrasonographic measurement in the diagnosis of acute rejection*

	Biopsy	
	Rejection ($n = 49$)	Non-rejection ($n = 31$)
Rise in transplant cross-sectional area (%)		
≥10	39	7
<10	10	24
Accuracy statistics		
Sensitivity	39 of 49 (80)	
Specificity	24 of 31 (77)	
Positive predictive value	39 of 46 (85)	
Negative predictive value	24 of 34 (71)	
Overall accuracy	63 of 80 (79)	

Values in parentheses are percentages

Table 2 *Predicted probability of rejection derived from ultrasonographic measurement*

Rise in transplant cross-sectional area (%)	Cumulative probability of rejection (%)*
10	53 (41–65)
15	73 (60–83)
20	87 (75–94)
25	94 (85–98)
30	97 (91–99)

*Values are mean (95 per cent confidence interval)

The probability of rejection exceeded 50 per cent when the transplant cross-sectional area had increased by greater than 8 per cent.

Histological analysis categorized the 49 rejection episodes as mild (15), moderate (26) or severe (eight). The relationship between histological severity and transplant swelling during rejection is shown in *Figure 3*. There was no statistically significant difference in the median (interquartile range) degree of swelling between mild (12·8 (0·0–17·5) per cent) and moderate (16·5 (13·2–21·5) per cent) rejection, but severe rejection (39·0 (28·3–55·0) per cent) was associated with significantly more swelling than that of either mild or moderate type ($P < 0·001$). *Figure 4* shows the significant correlation between the degree of impairment in renal function caused by rejection, expressed as the fall in estimated creatinine clearance

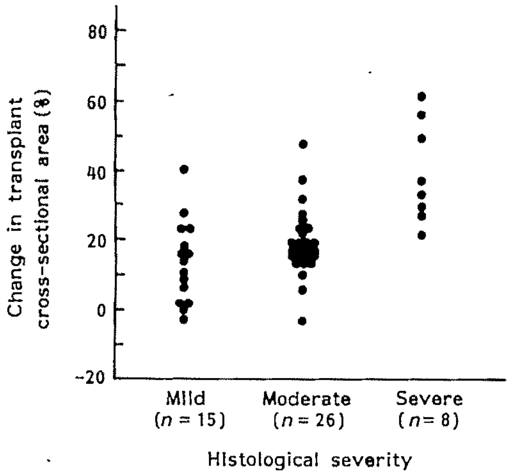

Figure 3 *Histological severity of rejection in relation to ultrasonographically measured change in transplant size*

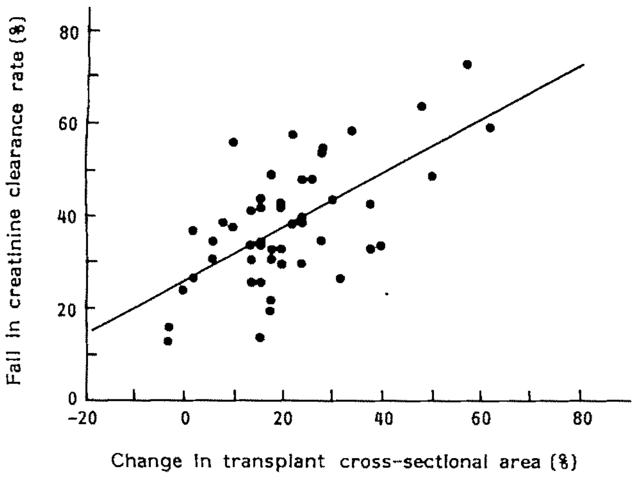

Figure 4 *Degree of impairment of renal function, expressed as the fall in creatinine clearance rate, in relation to ultrasonographically measured change in transplant size.* $r_S = 0.63$, $P < 0.001$

rate, and the degree of allograft swelling, expressed as the measured percentage change in transplant cross-sectional area ($r_S = 0.63$, $P < 0.001$).

No complication occurred in any patient as a result of the ultrasonographic monitoring carried out.

Discussion

The tomographic nature of ultrasonography, coupled with its absolute linearity of measurement, make it particularly suitable for the study of renal transplant size. The monitoring technique described is simple and non-invasive; it allows daily serial examination to be performed with ease and the results of the test are immediately available. Another major advantage is that the method uses technology that is widely available. It must be stressed, however, that real-time ultrasonography has been used for kidney transplant surveillance in this centre for several years and that all the scans have been performed by the same highly experienced transplant ultrasonographer using a dedicated machine.

In previous work it was demonstrated that an increase of ⩾10 per cent in transplant cross-sectional area was the best threshold in separating episodes of rejection from other causes of acute allograft dysfunction[1,3]. Although the usefulness of this threshold was confirmed in the present study, it remains rather arbitrary and, with the greater experience available for analysis, a predicted probability curve was generated by use of a logistic regression model. This allowed a probability of rejection to be assigned to each level of change in transplant cross-sectional area, which should prove more useful in clinical practice than the previous threshold of 10 per cent swelling.

Intrarenal manometry has been used by other centres in the diagnosis of acute renal allograft rejection[8–10]. Ultrasonographic measurement of transplant cross-sectional area and intrarenal manometry are estimating different parameters that reflect the same underlying process, namely the distension that occurs in the acutely rejecting renal transplant. In the present analysis ultrasonographic measurement yielded a sensitivity of 80 per cent, a specificity of 77 per cent, a positive predictive value of 85 per cent, a negative predictive value of 71 per cent and an overall accuracy of 79 per cent for the diagnosis of acute rejection. Taking an intrarenal pressure of 40 mmHg as the diagnostic threshold for rejection as described by Salaman and Griffin[9], the following statistics can be derived from their data: sensitivity 77 per cent, specificity 90 per cent, positive predictive value 71 per cent, negative predictive value 93 per cent and overall accuracy 87 per cent. Subsequent investigation in a different centre demonstrated a similar degree of accuracy but reported a lower power of discrimination for rejection occurring during delayed function caused by acute tubular necrosis[10]. Fine-needle aspiration cytology is used by some units for monitoring renal transplants and is undoubtedly a useful technique if local cytological expertise is available. Nevertheless, the accuracy of such cytology is not significantly different from that of ultrasonographic measurement of allograft swelling[11]. None of these three methods, intrarenal manometry, cytology and ultrasonography, meets the criteria of >80 per cent sensitivity and >90 per cent specificity that have been recommended as necessary for a useful diagnostic test[12]. However, as the accuracies of intrarenal manometry, cytology and ultrasonography seem broadly similar, the non-invasiveness and zero complication rate of the ultrasonographic technique deserve emphasis.

Doppler ultrasonography has also been proposed as a useful non-invasive technique in the assessment of renal transplant dysfunction[13,14]. Several quantitative indices have been used to describe the results of Doppler examination; a commonly used one, which increases during acute rejection, is the resistive index. Unfortunately, kidneys with delayed function secondary to acute tubular necrosis have been shown to have some of the highest values of resistive index and so this particular type of analysis does not have a high specificity in the diagnosis of acute rejection[15]. It is possible that an approach combining ultrasonographic measurement of transplant cross-sectional area with Doppler analysis of transplant blood flow could provide an even more useful non-invasive method of assessing transplant status.

Very little difference was found in the degree of transplant swelling during rejection graded as mild or moderate on histopathological grounds, but severe rejection was associated with significantly more swelling than that of mild or moderate type. Severe rejection proved relatively easy to diagnose histologically because of features such as vascular damage and interstitial haemorrhage, but the distinction between mild and moderate rejection was less certain, being based on a subjective estimate of the density of the same histological feature (mononuclear cell infiltrate). The present findings, therefore, reflect both the constraints of histological grading and the fact that the degree of severity of rejection is a continuum that, for ease of analysis, has been artificially divided into three. The functional severity of rejection was also studied and quantified by the creatinine clearance rate in preference to the serum creatinine level because the latter does not have a linear relationship with glomerular filtration rate and is therefore a less accurate index of renal function. A significant correlation was found between functional severity and transplant swelling during rejection, suggesting that ultrasonographic measurements can be usefully employed to judge the severity of a rejection episode; this may prove helpful in choosing antirejection therapy.

In conclusion, ultrasonographic measurement of renal transplant cross-sectional area has proved to be a simple and useful diagnostic test of acute rejection. The method has not replaced needle core biopsy, which is still used extensively in this unit. However, needle core biopsy is an invasive test associated with a small but important incidence of complications and this limits the frequency of its use. This limitation does not apply to ultrasonography. Serial ultrasonographic surveillance may be regarded as an adjunct to, rather than an alternative to, biopsy and may assume a role complementary to clinical examination of the patient with a transplanted kidney.

Acknowledgements

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Transrectal duplex colour Doppler ultrasonography of the prostate: a preliminary report

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Although transrectal ultrasonography is sensitive in detecting prostatic lesions in the peripheral zone, its specificity is low; biopsy of every suspicious lesion is required[1]. Biopsy improves the specificity of the test but also changes it into an invasive and expensive one. Previous studies have shown that Doppler ultrasonography may be useful in the differentiation between benign and malignant tumours of the breast and liver[2,3]. This study therefore assessed the vascularity of benign and malignant prostatic lesions using transrectal duplex colour Doppler scanning in an attempt to increase the specificity of the technique.

Patients and methods

A total of 29 patients of mean age 67 years referred for transrectal ultrasonography and/or prostatic biopsy were studied. All patients underwent digital rectal examination followed by standard transrectal ultrasonography and transrectal duplex colour Doppler scanning. Patients with an abnormal digital examination and/or abnormality on standard ultrasonography underwent systematic biopsy of each lobe of the gland. The presence of hypoechoic or hyperechoic areas and/or asymmetry of the prostatic lobes on transrectal ultrasonography was considered abnormal.

For the Doppler studies, an Aloka SSD680 scanner (Keymed, Southend, UK) was used with duplex and colour facilities and equipped with a 7·5-MHz linear probe. The Doppler filters were set to the minimum level (100 Hz), and the velocity range of the spectral display was set at 0·1–0·3 m/s. The presence of any persistent colour Doppler signal obtained in or around a lesion was recorded as a positive scan. The Doppler range gate was placed in or around any suspicious area to obtain the Doppler frequency shift spectral display. The resistive index (defined as the ratio of peak systolic frequency minus end-diastolic frequency to peak systolic frequency) was calculated from the frequency shift display, using the onboard computer software, by placing the calipers at the peak systolic frequency and at the end-diastolic frequency of a cardiac cycle.

Repeat transrectal ultrasonography was then performed using a Bruel and Kjær scanner (Nærum, Denmark) with a 7-MHz probe equipped with biopsy facility. Suspicious areas as assessed by the duplex colour scan were biopsied.

Informed consent was obtained and data analysed using the Mann–Whitney *U* test and Fisher's exact test.

Results

Twelve patients had histological evidence of malignancy, nine with bilateral lesions and three with carcinoma in one lobe and benign hyperplasia in the other. The remaining 17 patients had histologically proven benign hyperplasia or prostatitis. The results are summarized in *Table 1*.

Table 1 *Summary of results*

	Malignant lesions ($n = 21$)	Benign lesions ($n = 37$)
Histological analysis		
Poorly differentiated carcinoma	11	—
Well differentiated carcinoma	10	—
Benign prostatic hyperplasia	—	15
Prostatitis	—	22
Abnormal digital examination	16	15
Abnormal transrectal ultrasonography		
Hypoechoic	14	17
Hyperechoic	2	3
Mixed	3	1
Total	19	21
Abnormal digital examination or ultrasonography	19	24
Colour Doppler scan		
Positive	16	13
Negative	5	24
Mean(s.d.) resistive index	0·56(0·04)	0·55(0·07)

There was a significant difference in the number of positive colour Doppler scans between malignant and benign lesions ($P = 0{\cdot}006$). The specificity of a positive scan was 65 per cent and the positive predictive value 55 per cent. There was no significant difference in the resistive indices between benign and malignant lesions.

Discussion

A combination of digital rectal examination and transrectal ultrasonography increased the detection rate of lesions, but the non-specificity of the findings on standard ultrasonography is also confirmed in this study; benign and malignant lesions shared the same echogenic patterns. Although a higher proportion of positive colour Doppler scans was obtained in malignant compared with benign lesions, the method is still of limited value with a specificity of 65 per cent and a positive predictive value of only 55 per cent. Although angiogenesis is associated with neoplasia, benign inflammatory lesions (i.e. prostatitis) are also associated with hyperaemia[4]. The prolonged systolic phase and raised amplitude throughout the diastolic phase of the frequency shift waveform (indicative of a low-resistance bed) were demonstrated in both benign and malignant lesions. It is not surprising that no significant difference was noted in the resistive index values between the two groups. This overlapping of the Doppler parameters reduced the diagnostic power of the technique.

Although further studies are required, the preliminary results suggest that Doppler analysis does not confer enough additional data over standard ultrasonography to alter clinical management.

Acknowledgements

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Surgical workshop

Br. J. Surg. 1993, Vol. 80, August, 1064

'Belt loop' stitch

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Mechanical stapling devices are commonly used in colorectal surgery as they facilitate colorectal transection and anastomosis and shorten operating time. Purse-string applicators are less commonly employed in the creation of these anastomoses, although their usage decreases operating time further. The reason for this lack of use may be that purse strings inserted via an applicator are sometimes not applied regularly or may omit an appreciable length of the bowel circumference (*Figure 1*). Unevenly inserted purse strings may lead to a defective 'doughnut' on completion of a stapled end-to-end anastomosis and thus to anastomotic leakage, unless further reinforcing sutures are inserted. Defective purse strings are therefore usually removed and sutures reinserted manually. This manoeuvre prolongs operating time and can make the procedure more difficult as the end of the bowel with the defective purse string may need to be trimmed and thus shortened. Such experiences may account for the reluctance to insert purse strings with the aid of applicators because some surgeons consider that hand-suturing is a surer, albeit longer, method.

I use the purse-string applicator routinely even in low rectal anastomoses, finding that it is faster than manual insertion of purse strings. Furthermore, defective purse strings need not be removed but are easily salvaged by a 'belt loop' stitch as necessary.

Surgical technique

Belt loop stitches may be inserted along the circumference of the colon wherever the purse string has omitted a segment of the circumference of the bowel (*Figure 2*). These stitches hold the purse string in place much as a belt loop holds a pair of trousers securely around the waist. They ensure an evenly tied-down bowel end, which allows for a safe and secure stapled anastomosis. For use as the belt loop stitch 3/0 Vicryl (Ethicon, Somerville, New Jersey, USA) sutures have been found very suitable.

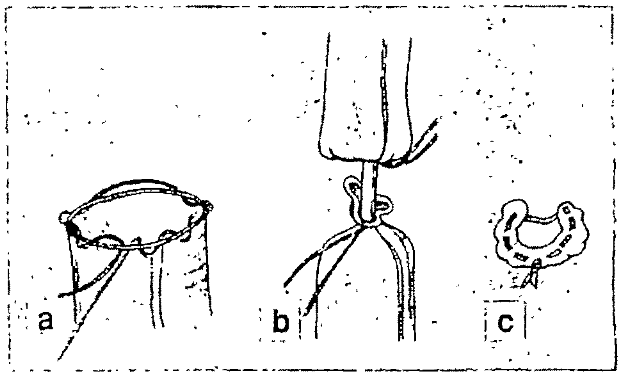

Figure 1 **a** *A purse string that is not suitably inserted, some segments of the bowel circumference being omitted.* **b** *Tying of such defective purse strings lead to uneven protrusion of the bowel end, which may make stapling unsafe.* **c** *Stapling in situations where a purse string is not regularly inserted leads to a defective 'doughnut'*

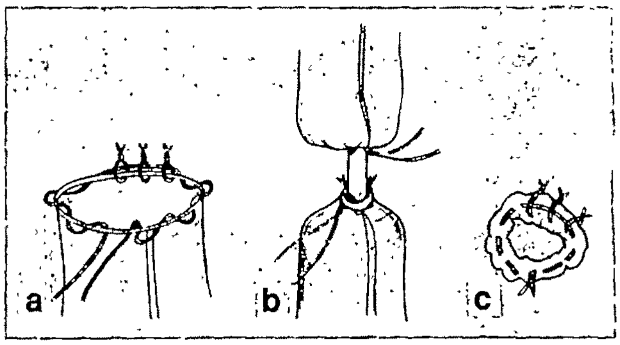

Figure 2 **a** *Belt loop stitches are inserted as required along the rim of the bowel end.* **b** *The belt loop stitch holds down the bowel end when the purse string is tightened and results in an even protrusion of the bowel end, which is then ready for stapling.* **c** *Use of the belt loop stitch results in a complete 'doughnut' after stapling*

Discussion

This simple method of inserting a belt loop stitch to salvage defective purse strings may permit the more confident and routine use of purse-string devices in stapled anastomoses.

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Fistula complicating restorative proctocolectomy

Twenty-seven patients developed a fistula after 168 restorative proctocolectomies. Thirteen fistulas were enterocutaneous (two with communication to the bladder); their origins were from the pouch (three patients), the ileoanal anastomosis (three), the pouch appendage (three), a previous loop ileostomy (two) and iatrogenic small bowel injury (two). Two patients had Crohn's disease. The pouch was removed in four patients, one of whom died from chronic small bowel obstruction; the remaining nine have satisfactory pouch function after fistula excision. Ten pouch–vaginal fistulas occurred, all from the ileoanal anastomosis; four were extrasphincteric. Four of these patients had underlying Crohn's disease. Only two patients, with Crohn's disease and indeterminate colitis, required pouch excision; the remainder have good pouch function after treatment of the fistula. There were three pouch–perineal fistulas, all from the ileoanal anastomosis; these were successfully managed by seton fistulotomy. There was one pouch–vesical fistula, successfully treated by excision of the fistula and pouch appendage.

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Pouch construction in restorative proctocolectomy may be complicated by sepsis and anastomotic breakdown. In some patients these complications result in pouch-related fistulas. Pouch–vaginal fistula is now a recognized event, particularly if there is localized ischaemia, entrapment in stapling devices, anastomotic breakdown, undisclosed Crohn's disease or operative damage to the vagina[1–3]. Pouch–cutaneous fistula has also been reported, resulting from leaks in the pouch, at the ileoanal anastomosis and from the ileostomy closure sites, and iatrogenic damage to the small bowel[4,5].

The origin, management and outcome of patients with such fistulas are described.

Patients and methods

A total of 168 restorative proctocolectomies were performed between 1984 and 1992. The underlying diagnoses were ulcerative colitis (103 patients), indeterminate colitis (ten), Crohn's disease (ten), familial adenomatous polyposis (26), slow-transit constipation after failed ileorectal anastomosis (eight), megacolon with megarectum (ten) and dysplasia with multiple polyps (one). Details of this series have been published previously[6]. Following these operations 27 patients developed a fistula: 13 were enterocutaneous (two connected to the bladder), ten pouch–vaginal (four mid-septal or high fistulas), three pouch–perineal and one pouch–vesical.

Results

Pouch–cutaneous fistula

Thirteen patients developed a pouch–cutaneous fistula (*Table 1*). Eight occurred in patients undergoing the first 50 operations in the series, four in the second 50 and only one in the final 68.

One early fistula complicated breakdown of an unprotected totally stapled restorative proctocolectomy and was managed successfully by pelvic drainage and loop ileostomy, which was subsequently closed. The remainder all presented some months, and in four cases >1 year, after pouch construction. All except two of these patients had had a covering loop ileostomy.

Of the 12 late fistulas, two originated from the ileoanal anastomosis (both sutured), three from the pouch itself (all sutured pouch constructions), three from the apex of a J pouch appendage, one from a previous small bowel anastomosis, two from iatrogenic small bowel damage following difficult operations for intestinal obstruction and one from the site of loop ileostomy closure. In seven patients there was persistent narrowing at the ileoanal anastomosis, which may have contributed to the pathogenesis of the fistula. In two of the fistulas from the J pouch appendage there was a communication

Table 1 *Clinical features of 13 patients with pouch–cutaneous fistula*

	No. of patients
Underlying diagnosis	
Ulcerative colitis	9
Crohn's disease	2
Megacolon and megarectum	2
Previous colectomy	13
Covering ileostomy	10
Origin of fistula	
Small bowel anastomosis	1
Iatrogenic damage to small bowel at laparotomy	1
Small bowel following loop ileostomy closure	2
Pouch suture line	3 (2 all sutured)
Pouch appendage	3 (2 communicated with bladder)
Ileoanal anastomosis	3 (2 sutured, 1 stapled)
Other factors in pathogenesis*	
Chronic small bowel obstruction	3
Chronic pelvic sepsis	3
Stenosis at ileoanal anastomosis	7
Mid-pouch stenosis	1
Diabetes mellitus	1
Ankylosing spondylitis	1
Treatment	
Pouch excision	4 (2 Crohn's disease)
Proximal diversion alone	3
Excision of fistula	6 (pouch appendage excised in 2)

*More than one factor was present in some patients

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Table 2 *Clinical features of ten patients with pouch–vaginal fistula*

	No. of patients
Underlying diagnosis	
Ulcerative colitis	5
Crohn's disease	4
Indeterminate colitis	1
Previous colectomy	5
Covering ileostomy	5
Origin of fistula	
Ileoanal anastomosis	10 (3 sutured, 7 stapled)
Type of fistula	
Intersphincteric	1
Trans-sphincteric	4
Suprasphincteric	1
Extrasphincteric	4
Other factors in pathogenesis*	
Recurrent pouchitis	5
Long afferent limb and ileoanal stenosis	1
Chronic pelvic sepsis	2
Retained diseased rectum below 'ileoanal' anastomosis	1
Stenosis at ileoanal anastomosis	3
Treatment	
Pouch excision	2 (1 Crohn's disease, 1 indeterminate colitis)
Fistula excision and reanastomosis at the dentate line	1
Proximal diversion alone	1
Mucosal advancement	1
Seton fistulotomy	4
Fistula laid open	1

*More than one factor was present in some patients

to the bladder that had been recognized clinically by recurrent urinary tract infection and pneumaturia.

Two of the late fistulas occurred in patients in whom the underlying diagnosis is now known to be Crohn's disease. Two further fistulas occurred in patients undergoing restorative proctocolectomy for megacolon and megarectum. Other factors that may have contributed to fistula formation included chronic pelvic sepsis in three patients, chronic small bowel obstruction in three, mid-pouch stenosis in one and diabetes mellitus in one.

Four patients have had the pouch removed: the two with Crohn's disease and enterocutaneous fistula, one with chronic obstruction resulting from a long efferent limb in an S pouch complicated by a fistula, and a patient who did not want a reconstruction procedure. The patient with an S pouch complicated by fistula treated by excision developed small bowel obstruction and septicaemia 2 months after pouch removal, from which she died. Three leaks (one early) from the ileoanal anastomosis were managed by raising a loop ileostomy, which has subsequently been closed. The remaining six patients have all had an operation to excise the fistula track. In two cases this included amputation of the pouch appendage, and in both the bladder defect was also closed. Only two of these procedures were covered by a loop ileostomy and all were successful. All nine patients who have retained the pouch have normal continence and good reservoir function.

Pouch–vesical fistula

One patient presented with septicaemia 1 year after pouch construction. He complained of pneumaturia and recurrent urinary tract infection. Repeated radiological examination failed to detect a fistula but cystoscopy confirmed a communication to the bowel. Reoperation indicated that the fistula was arising from the site of previous loop ileostomy closure, but there was also a communication to a long J pouch appendage and to the dome of the bladder. The fistulas and pouch appendage were excised and the bladder defect closed without a loop ileostomy. The patient has excellent pouch function.

Pouch–vaginal fistula

Ten patients developed a pouch–vaginal fistula (*Table 2*): three in the first 50 operations in the series, four in the second 50 and three in the final 68.

One patient was referred to the unit after totally stapled restorative proctocolectomy without a covering loop ileostomy performed elsewhere. This had been complicated 2 weeks after operation by a vaginal fistula requiring a loop ileostomy. Investigation revealed a chronic pelvic abscess and 4 cm of residual rectum below the presumed ileoanal anastomosis with a fistula from the anastomosis to the posterior fornix. Reoperation involved resection of the residual rectum and a new sutured ileoanal anastomosis at the dentate line. Following loop ileostomy closure this patient has normal pouch function.

One other early pouch–vaginal fistula also occurred to the posterior fornix after a totally stapled restorative proctocolectomy without a covering ileostomy. This fistula was probably the result of operative trauma to the vagina or entrapment during stapled ileoanal anastomosis. The fistula was managed by raising a loop ileostomy; this was closed 3 months later when the fistula had completely healed. This patient has a satisfactory functional result.

The remaining eight pouch–vaginal fistulas all occurred 6 months to 2 years after operation. Four fistulas occurred in patients who were later found to have Crohn's disease. One of these patients had developed a pelvic abscess after synchronous colectomy and totally stapled restorative proctocolectomy; the fistula became evident after closure of the loop ileostomy 5 months later. This patient has now had the pouch excised because of persistent pelvic sepsis and severe anal stenosis, complicating perianal Crohn's disease. The other three patients with Crohn's disease have been successfully managed by operation: one has had a vaginal advancement flap with a covering loop ileostomy for an extrasphincteric mid-septal fistula; the other two, both with trans-sphincteric fistulas, were managed by a cutting seton fistulotomy.

One further patient, without Crohn's disease, eventually underwent pouch excision. This patient had indeterminate colitis and developed a suprasphincteric fistula 2 years after pouch construction. The fistula was excised and the sphincter successfully repaired but, because of progressive anal stenosis requiring intubation, the pouch was removed from the pelvis and a reservoir ileostomy constructed.

Two trans-sphincteric fistulas were treated by cutting seton fistulotomy, and one patient with an intersphincteric track was treated by laying open the fistula.

So far, none of these fistulas has recurred and all patients have excellent pouch function, except for one who has intermittent soiling.

Pouch–perineal fistula

Three patients developed a pouch–perineal fistula after restorative proctocolectomy. Two underwent pouch construction without a covering ileostomy.

One was a diabetic patient who had already had a history of perianal sepsis. He developed a trans-sphincteric fistula after operation that was managed by cutting seton fistulotomy. Another patient developed an extrasphincteric fistula from a stapled ileoanal anastomosis after restorative proctocolectomy without a covering ileostomy. This was managed by cutting seton fistulotomy and a loop ileostomy, which has now been successfully closed with a satisfactory functional outcome. The third patient developed a trans-sphincteric fistula following drainage of an ischiorectal abscess 7 years after pouch construction for slow-transit constipation using a sutured ileoanal anastomosis. She has been managed by cutting seton fistulotomy and has normal pouch function.

Discussion

Some form of fistula complicated pouch construction in 27 of 168 patients (16 per cent). Despite this, 21 of the patients have satisfactory pouch function. Although pouch–cutaneous fistula seems to have become less common with increasing experience of the operation, suggesting that one of the factors in the pathogenesis is technical, this does not hold true for pouch–vaginal fistula, which had a uniform incidence throughout the series.

Pouch–cutaneous fistula seems to arise from disruption of the ileoanal anastomosis, from a suture line in the pouch, from a long J pouch appendage, as a result of leakage from an ileostomy closure site or from iatrogenic damage to the small bowel during secondary laparotomy. With the introduction of stapling techniques these complications appear to have become less common[7,8]. Many would argue that loop ileostomy protects patients from these potential complications[9]. The use of a loop ileostomy might have prevented one pouch–cutaneous fistula, one pouch–perineal fistula and two pouch–vaginal fistulas. Nevertheless a trial of loop ileostomy by the present authors[10] did not support this contention, and there are many who now believe that the complications of loop ileostomy outweigh the risk of anastomotic leakage[10–12]. Furthermore, in the present series at least two fistulas arose from the loop ileostomy site. One clear message from the present study is that a long J pouch appendage should be avoided; if one is present after pouch construction it should probably be amputated. Surprisingly, pouch–cutaneous fistula was not prominent[6] in the ten patients with Crohn's disease in the entire series of 168.

Pouch–vaginal fistula does not appear to be related to surgical technique or experience. It was particularly common (40 per cent) in patients who were eventually found to have Crohn's disease. Nevertheless, pouch excision has so far been necessary in only one. The only other patient with a successfully treated pouch–vaginal fistula who required pouch excision had indeterminate colitis and developed a tight stenosis at the ileoanal anastomosis. It is not advisable to perform restorative proctocolectomy in patients known to have Crohn's disease. Some pouch–vaginal fistulas result from early breakdown of the ileoanal anastomosis. Others may be caused by operative or diathermy injury to the vagina during proctocolectomy. It has been suggested that entrapment of a portion of the vagina in the circular stapling device might be responsible for a fistula. Some undoubtedly result from an early postoperative pelvic abscess.

It is more difficult to explain the low trans-sphincteric pouch–vaginal fistula that occurs months or even years after pouch construction. We believe that some of these may result from reactivation of intersphincteric sepsis from cryptoglandular infection. Irrespective of the cause of these low fistulas, most can be managed easily by a cutting seton which may be tightened in the outpatient clinic by application of rubber bands[13].

It may not be possible to treat mid-septal vaginal fistula by anal advancement flaps because of anal fibrosis; a vaginal advancement may be more appropriate under these circumstances. For high vaginal fistula in the absence of pelvic sepsis or Crohn's disease, division of the stapled ileoanal anastomosis and subsequent suture of the ileum to the anus at the dentate line may resolve the problem.

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Short note

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Bile acid absorption after restorative proctocolectomy

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Restorative proctocolectomy with ileal pouch formation results in stasis of intestinal contents with bacterial overgrowth and altered bile acid metabolism in the terminal ileum[1]. Structural changes such as villus atrophy and a chronic inflammatory infiltrate are also common[2]. The impact of the operation on the metabolic function of the ileal mucosa remains unclear. The terminal ileum possesses a specialized system for active bile acid reabsorption that maintains the enterohepatic circulation. Disturbance of bile acid absorption may result in a reduced bile acid pool, fat malabsorption and altered lithogenicity of gallbladder bile. This study used a miniature flux chamber technique[3] to examine the influence of restorative proctocolectomy on active ileal mucosa bile acid absorption.

Patients and methods

Patients undergoing surgery for ulcerative colitis ($n = 24$), familial adenomatous polyposis (FAP; $n = 10$), constipation ($n = 11$) or colonic cancer ($n = 6$) were studied. Bile acid absorption was measured at the time of colectomy using tissue from the distal 2 cm of ileum. This was compared with results from ileal pouch biopsy material from 37 patients, taken a median of 8 (range 4–72) months after restorative proctocolectomy with a J pouch. Pouch mucosal biopsies were obtained in the outpatient clinic using Officer's biopsy forceps. All patients had a satisfactorily functioning pouch with no suspicion of Crohn's disease or pouchitis at the time of biopsy.

Sequential studies were performed in 15 patients before and after restorative proctocolectomy.

Studies were conducted using a miniature flux chamber technique that has been extensively validated[3]. Bile acid kinetic data are presented as tissue uptake of taurocholic acid and as the transport of taurocholic acid from mucosal to serosal compartments of the chamber on a tissue wet weight basis.

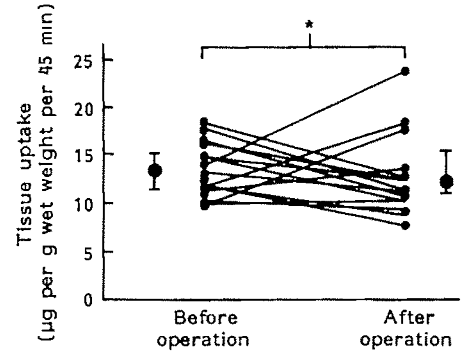

Figure 1 *Ileal bile acid uptake before and after restorative proctocolectomy in 15 patients. Bars are median (95 per cent confidence interval).* *P = *0·48* (*Wilcoxon rank sum test*)

Table 1 *Bile acid uptake and transport across ileal mucosa*

	Uptake	Transport
Ulcerative colitis ($n = 24$)	13·8 (12·4–15·4)	1·1 (0·7–1·5)
Familial adenomatous polyposis ($n = 10$)	12·8 (10·5–15·0)	0·8 (0·3–1·4)
Constipation ($n = 11$)	14·4 (11·5–17·4)	0·6 (0·3–1·2)
Cancer ($n = 6$)	13·8 (6·6–17·3)	0·8 (0·2–2·6)
Established pouch ($n = 37$)	13·4 (11·7–15·1)	1·0 (0·7–2·0)

Values are median (95 per cent confidence interval) in µg per g tissue wet weight per 45 min

Results

There were no significant differences in ileal uptake or transport of taurocholic acid between patients at least 4 months after restorative proctocolectomy and controls with ulcerative colitis, FAP, constipation or cancer (*Table 1*). In patients studied sequentially before and at least 4 months after restorative proctocolectomy, bile acid tissue uptake (*Figure 1*; $n = 15$) and transport ($n = 7$) were not significantly different (Wilcoxon rank sum test).

Discussion

Faecal bile acid loss in patients with an ileostomy or pouch has been reported to be 1·5 times that in healthy controls[4]. Impaired ileal absorption, as measured by the Schilling test and ^{14}C faecal excretion, has previously been reported in patients following ileal pouch–anal anastomosis[5]. Using ^{75}Se-labelled homotaurocholate, which more closely measures active ileal bile acid transport, no difference was found between patients with an ileal pouch and those with an end ileostomy[6]. The significant differences found between controls with an intact colon and patients with a pouch may result from an increased transit time or bacterial colonization rather than an alteration in ileal function.

The present study, performed on established pouches a median of 8 (range 4–72) months after restorative proctocolectomy, demonstrates that the ability of pouch ileal mucosa to absorb taurocholic acid actively (the bile acid most dependent on active transport mechanisms) is similar to that of terminal ileum in patients undergoing surgery for ulcerative colitis, FAP, constipation or colonic cancer. Sequential studies in tissue from patients before and after pouch formation showed no significant impairment.

It is concluded that pouch formation does not significantly alter the ability of ileal mucosa to absorb bile acids. However, in the present study there were individual patients in whom bile acid absorption was at the lower end of the range and who may represent a subset at risk of increased bile acid loss.

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Case report

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Crohn's disease involving a rectus abdominis myocutaneous flap

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Cutaneous Crohn's disease of the perineum is a well recognized problem for which treatment is difficult; options include myocutaneous flaps to provide cover of cavities following sinus and fistula surgery[1]. A patient is presented in whom Crohn's disease spread to include the normal skin of a pedicled myocutaneous flap that had been harvested from an area distant from the Crohn's disease. This case is believed to be the first such reported.

Case report

A 60-year-old woman who had had severe Crohn's disease for many years previously underwent staged panproctocolectomy and formation of an ileostomy. She presented with two long-standing and painful vaginoperineal sinuses; histological proof of cutaneous perineal Crohn's disease was obtained. The sinuses were widely excised and the resulting abdominoperineal defect closed using an inferiorly based myocutaneous flap from the left rectus abdominis muscle. A skin island was included with the flap to fill the cavity, the skin edges being sutured to the healthy perineal skin.

The patient fared well after operation but was readmitted 5 months later with perineal pain and vaginal discharge. Examination under anaesthesia revealed longitudinal ulcers on either side of and involving the skin flap. Biopsies of the ulcers showed Crohn's disease within the skin of the myocutaneous flap. The woman also developed a recurrent perineal sinus with a track to the ischial tuberosity; a further operation was undertaken to excise the sinus and the ulcers on either side of the skin island. Histological analysis of the excised tissue again showed granulomatous inflammation consistent with Crohn's disease in the skin of the myocutaneous flap.

Discussion

Crohn's disease has two broad types of cutaneous manifestation[2]. The first includes a wide variety of conditions such as erythema nodosum, pyoderma gangrenosum and polyarteritis nodosa. The second comprises granulomatous lesions as a direct extension of the disease process on to the skin, for example in perianal and perineal lesions, and in fistula tracks, often after operation. Severe perineal Crohn's disease may give rise to complex fistulas requiring wide excision of the subcutaneous tissue and skin, resulting in a large cavity. Myocutaneous flaps have been successfully used to treat these wounds[3]. Use of the rectus abdominis myocutaneous flap has become widespread, as this method is reliable and provides good bulk[1,3].

The present case is remarkable in that the healthy skin of the myocutaneous flap developed histological evidence of Crohn's disease. This indicates a degree of 'invasiveness' of the disease not previously noted. There have been reports in the literature of other disease processes affecting pedicled myocutaneous flaps. Acne vulgaris appeared in the skin island of a latissimus dorsi flap used for breast reconstruction[4], despite the fact that there had been no active acne for 25 years. Tumour spread within myocutaneous flaps has also been reported, but is extremely rare[5]. Several cases of tumour recurrence have been reported in which chest wall metastases were observed at the vascular pedicles of various myocutaneous flaps. In these cases the tumour migrated into the pedicle of the flap, presumably via lymphatic or vascular spread, rather than into the skin island.

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Relationship between intra-abdominal and intrarectal pressure in the proctometrogram

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During normal defaecation the intrarectal pressure increases but, in the absence of a reference catheter in the pelvis, the contribution of abdominal straining and rectal contraction to this rise is unclear. Anorectal manometry was performed in ten consecutive women with no gastrointestinal symptoms in an attempt to measure intrapelvic pressure using a catheter in the bladder. During filling the mean(s.e.m.) rectal pressure increased from 2(1) to 18(4) cmH$_2$O. The mean(s.e.m.) intravesical pressure remained unchanged at 2(1) cmH$_2$O. Evacuation of the rectal balloon produced an increase in mean(s.e.m.) intrarectal pressure from 18(4) (end-filling pressure) to 68(15) cmH$_2$O. The mean(s.e.m.) intravesical pressure increased from 2(1) to 51(18) cmH$_2$O. The true intrarectal pressure (intrarectal minus intravesical) did not rise during defaecation. The rise in intrarectal pressure during rectal evacuation occurs by increased intrapelvic pressure alone.

Since the description of the balloon proctogram[1], increasing attention has been focused on rectal dynamics. Rectal sensation, compliance, volume to produce call to stool and maximum tolerated volume have become parameters of interest in several conditions[2–4]. These studies have been performed without the benefit of a reference catheter in the pelvis and therefore the relative contribution of abdominal straining and rectal contraction to the evacuation phase of the proctometrogram is unclear. Urologists have used the rectum as a site for a reference catheter and have identified a role for detrusor contraction in normal micturition[5]. A similar role for the rectum is presumed but has not been described.

The aim of this study was to use the empty bladder as a reference for intrapelvic pressure and to establish the importance of rectal contraction in defaecation.

Patients and methods

Approval for the study was granted by the local ethical committee. Ten women undergoing urodynamics for urinary symptoms were studied. All patients were free from gastrointestinal symptoms and did not suffer from constipation. Only patients with stable detrusor filling profiles were studied as the output from an unstable reference catheter could have been interpreted as rectal activity. After performing standard urodynamics, the bladder was drained completely. With the patient seated, the rectum was then distended at a rate of 40 ml/min via a double-lumen 8-Fr catheter placed inside a condom. Patients were asked to indicate when a call to stool was observed. Rectal filling was stopped and, after a short observation period, patients were asked to evacuate the water-filled balloon from the rectum. Before rectal filling, Valsalva's manoeuvre was performed to confirm that the rectal and bladder manometry catheters produced similar pressure rises. Data were recorded on a Dantec Disa six-channel recorder (type 31C40) using a Dantec Disa two-channel water-perfusion catheter (Dantec Electronics, Bristol, UK). Results were analysed using Student's *t* test.

Results

Before rectal filling, Valsalva's manoeuvre produced a mean(s.e.m.) rise in intrarectal and intravesical pressures to 77·7(5·7) and 80·0(5·8) cmH$_2$O respectively ($P = 0{\cdot}33$).

The mean(s.e.m.) instilled volume required for a call to stool was 96(28) ml. During filling, the mean(s.e.m.) rectal pressure increased from 2(1) to 18(4) cmH$_2$O. The mean(s.e.m.) intravesical (intrapelvic) pressure remained unchanged at 2(1) cmH$_2$O. All patients were able to evacuate the rectal balloon without difficulty. During evacuation of the balloon, the mean(s.e.m.) intrarectal pressure increased from 18(4) (end-filling pressure) to 68(15) cmH$_2$O. The mean(s.e.m.) intravesical pressure increased from 2(1) to 51(18) cmH$_2$O. The true intrarectal pressure (intrarectal minus intravesical) did not rise during defaecation and indeed fell before evacuation of the balloon (*Figure 1*).

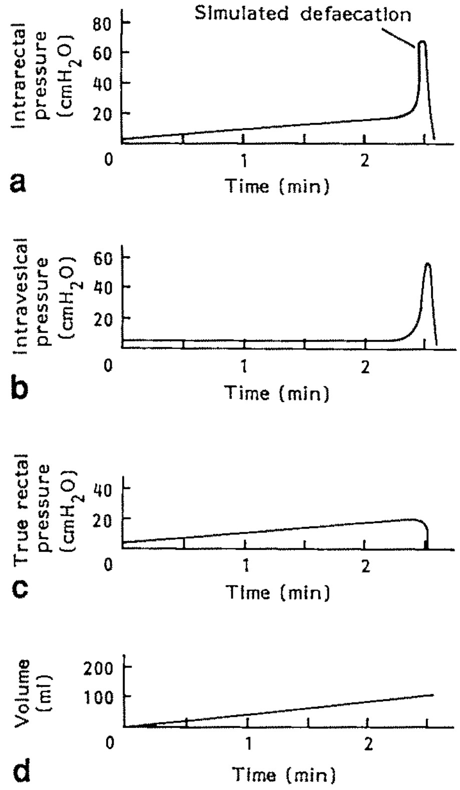

Figure 1 *Mean pressure changes during filling and evacuation of a rectal balloon.* **a** *Intrarectal pressure, showing simulated defaecation at 2 min 30 s;* **b** *intravesical pressure;* **c** *true rectal pressure (intrarectal minus intravesical pressure);* **d** *volume of the balloon in the rectum*

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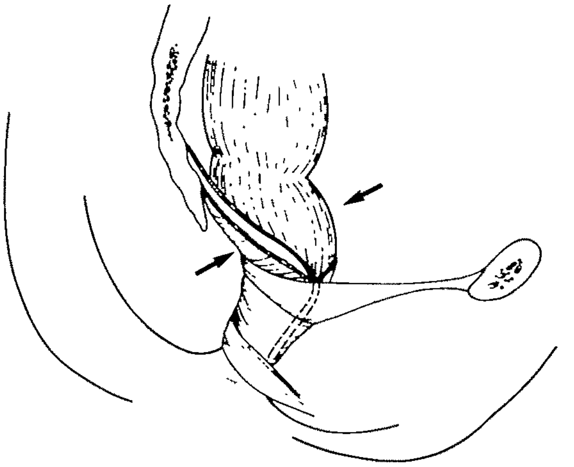

Figure 2 *Effect of extraneous pressure (arrows) on the lower rectum*

Discussion

By using a reference catheter placed outside the bladder, urodynamic studies can measure true detrusor contraction. This allows the diagnosis of contraction problems such as detrusor instability or bladder atony. Proctologists have previously concentrated on the filling phase of rectodynamics and have not looked closely at rectal contractility during evacuation. The contribution of rectal contraction to defaecation was not known. By placing a reference catheter in the bladder, the influence of intra-abdominal pressure was countered and rectal activity alone was studied.

The results suggest that increases in intrarectal pressure seen during the evacuation phase of the proctometrogram result from raised intra-abdominal pressure alone; the rectum is squeezed between raised intra-abdominal pressure and a contracting pelvic floor (*Figure 2*).

Although the rectal and bladder catheters gave slightly different pressures during Valsalva's manoeuvre, the difference was not significant and unlikely to account for the observation. Previous studies have demonstrated that similar pressures are recorded in the rectum, bladder and posterior fornix of the vagina during intra-abdominal straining, and these sites can therefore be used as suitable reference points for urodynamics or rectodynamics[6].

During rectal evacuation the true intrarectal pressure did not rise and indeed appeared to fall. This reduction in pressure is unlikely to result from relaxation of the internal sphincter alone as the water-perfusion catheter lying within the condom reflects pressure changes within the rectum and not the adjacent sphincter. Although rectal accommodation could account for a slight reduction in rectal pressure, this was not seen, probably reflecting the slow infusion rate used.

The present findings suggest that the lower rectum may relax during defaecation and contract as a secondary event consistent with the peristaltic reflex seen in the adjacent colon. The manometry catheter was evacuated with the rectal balloon and this phase of defaecation was not recorded.

Peristalsis comprises a wave of relaxation, thought to be mediated by non-adrenergic non-cholinergic nerves, followed by a cholinergic contraction[7]. The observation that the lower rectum initially relaxes during balloon evacuation is consistent with current thinking on colonic physiology.

If the evacuation phase of the proctometrogram does represent normal physiology, then the key to defaecation may lie in relaxation and not contraction of the rectum, the force for which derives from intra-abdominal pressure alone.

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Short note

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Histological and microbiological assessment of the role of micro-organisms in chronic anal fistula

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Infection would seem to be an integral part of the pathogenesis of fistula *in ano*[1]. The microbiology of acute anorectal sepsis is well documented[2,3], but the only study on chronic anal fistula raised doubts about the relevance of infection in fistula persistence[4]. The present histological study complements the earlier work, which used microbiological methods alone and might have overlooked important organisms.

Patients and methods

Granulation tissue from eight patients with non-specific fistula *in ano* was processed within 4 h of surgery. Three samples from the intersphincteric part of the fistula were obtained.

Two samples were studied microbiologically, employing methods described previously[4], to allow comparison between the relative density of micro-organisms in culture with that on histological specimens. Any discrepancy might suggest the presence of an important organism that proves difficult to culture and identify.

The third sample was fixed in 10 per cent formal saline for histological processing. Multiple 4-μm paraffin sections were stained using haematoxylin and eosin, Gram, cresyl fast violet, periodic acid–Schiff and Ziehl–Neelsen stains.

Results

Microbiology (Table 1)

The eight fistula specimens grew gut organisms of similar variety and number, as documented previously[4]. No organisms were grown at the 10^6 dilution. In seven specimens there were fewer than ten colonies for each species cultured; in one specimen there were more than 50 colonies of each of seven species. No *Mycobacterium* species was grown from any of the eight specimens.

Table 1 *Bacterial isolates for eight anal fistulas*

	No. of isolates per 0·1 ml tissue			
	Enrichment medium	Undiluted	10^3 dilution	Total
Aerobic and facultative bacteria				
Gram-negative bacteria				
Escherichia coli	7	7	3	17
Gram-positive bacteria				
Enterococcus spp.	4	4	1	9
Streptococcus viridans	3	4	2	9
Coagulase-negative staphylococci	2	2	1	5
Group F streptococci	1	2	1	4
Group B streptococci	1	0	0	1
Bacillus spp.	2	1	0	3
Corynebacterium spp.	0	1	0	1
Anaerobic bacteria				
Gram-negative bacteria				
Bacteroides fragilis	3	3	1	7
Fusobacterium spp.	2	2	0	4
Gram-positive bacteria				
Clostridium spp. (not *C. perfringens*)	6	6	0	12
Peptostreptococcus spp.	5	5	1	11
Gardenerella vaginalis	0	1	0	1
Bifidobacterium spp.	1	0	0	1
Total	37	38	10	85

Histology

Sections of tissue from all eight specimens showed a similar pattern of intense active chronic inflammatory change characterized by large numbers of plasma cells, scattered multinucleate foreign-body giant cells and prominent vascular proliferation. Acute inflammatory change (of variable degree) was superimposed. No granulomas were seen in any specimen. Vegetable matter was demonstrated on the granulation tissue surface in one specimen only and bacteria were seen on histological examination and subsequent Gram staining. Relatively large numbers of organisms were grown from this specimen.

Stains for *Helicobacter* species, *Mycobacterium tuberculosis* and fungi were negative in all specimens.

Discussion

The present study has confirmed the relative paucity of cultured organisms and demonstrates that this does not occur because of methodological problems since histological examination did not reveal many organisms. However, micro-organisms might be difficult to grow and to see histologically.

In other circumstances, histological examination has been used to demonstrate important pathogens such as *M. tuberculosis*, *M. leprae* and *H. pylori*. Histological studies have established an important pathological role for the last two organisms.

In conclusion, there is little evidence to support the role of infection in fistula persistence. Other explanations should be sought.

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Profiles of workload in general surgery from linked hospital statistics

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Data from the Oxford Record Linkage Study between 1976 and 1986 were used to analyse statistical profiles of hospital care, taking account of multiple admissions per patient. Admission rates were higher in the elderly than the young, they were higher for men than women, and they increased over time. Episode-based admission rates increased by 15·5 per cent and person-based rates by 11·6 per cent. Most of the increase therefore represented a real rise in the number of people treated rather than an increase in multiple admissions per person. In the latest year of the study there was a mean of 125 admissions per annum per 100 male patients admitted and of 118 admissions per annum per 100 female patients admitted. The mean length of stay per admission and the total time spent in hospital per person per annum declined substantially from 1976 to 1986. Admission rates for prostatectomy, colectomy and varicose vein surgery increased significantly and those for appendicectomy, cholecystectomy and peptic ulcer decreased significantly.

The importance of statistical analysis of clinical workload has increased for several reasons, including the widespread use of medical audit, recognition of the value of quantified information about workload relating to provision of healthcare and its resources, the requirement for health authorities to identify needs for services and develop contracts for purchasing care, and the requirement for clinical providers of care, as partners to contracting, to understand demographic and population-based profiles of care.

Statistics from routine hospital information systems, such as the Hospital In-patient Enquiry[1] and the hospital episode system, while lacking the detail that may be recorded in clinical departmental audit systems[2], can be used to provide a statistical perspective related to large defined populations. These routine hospital statistics are episode rather than person based and two or more admissions for the same person are counted separately. It is usually impossible to distinguish the numbers of people in receipt of care from the total episodes of care. This restricts the value of the statistics, and increases in the rates of inpatient admission to acute hospitals (about 2 per cent annually in England during the 1970s and 1980s[3]) are difficult to interpret without linked statistics. Increases may reflect a change in the incidence of disease, lowered clinical thresholds for admission, an increase in the availability of effective forms of treatment, or an increase in multiple admissions to hospital per person.

The Oxford Record Linkage Study has been used to analyse multiple admissions per person by linking together successive episodes relating to the same individual within a specialty[4–7]. This paper reports person-based admission rates, readmission rates, lengths of stay and some aspects of clinical caseload in general surgery.

Patients and methods

The Oxford Record Linkage Study is a collection of abstracts of hospital inpatient records (including day cases), birth registrations and death certificates. The data have been collected so that records relating to the same person can be linked[8,9]. The analyses presented relate to people who were resident and treated in the six districts of the Oxford region between 1976 and 1986.

Trends were analysed in episode- and person-based admission rates to general surgery, including urology. Patterns of emergency readmission were analysed. An emergency readmission was defined as any subsequent hospital episode, coded as an emergency, to any specialty within 28 days of discharge from general surgery. The method used and its rationale have been discussed previously[10]. Multiple admissions, mean lengths of stay and total days spent in hospital were calculated. Admission rates in the specialty were analysed for diagnoses and operations. These were coded in the record linkage study according to the eighth and ninth revisions of the International Classification of Diseases[11,12] and the operations codes of the Office of Population Censuses and Surveys[13].

The diagnoses and operations analysed were those recorded as the main diagnosis or operation on each hospital record. Trends over time were studied by fitting a regression equation to the trend in admission rates and calculating the mean annual rate of change (by using the log of the rates) with its 95 per cent confidence interval[14].

The population of the Oxford region has grown because of natural increase (numbers of births minus deaths), net inward migration[15] and an increase in the number of elderly people. All-age admission rates over time (which show trends in actual workload) and age-standardized rates (which show trends after adjustment for changes in the age structure of the population) were compared. Rates were standardized by the direct method, using admission rates in 1981 as the standard population.

Data from the Oxford Cancer Registry were analysed to obtain information on the incidence of common cancers treated by general surgeons.

Results

Person-based age-specific hospital admission rates for male and female patients in 1976 and 1986 are shown in *Figure 1*. Admission rates were higher in the elderly than the young, higher in males than females, and increased over time. The most striking increases occurred in the oldest male age groups.

The mean numbers of admissions per 100 patients admitted to general surgery are shown in *Table 1*. The data show the extent to which routine episode-based health service statistics were inflated by multiple counting of successive episodes for the same person. In 1976 a total of 39 153 admissions occurred for 33 006 people, while in 1986 there were 48 551 admissions for 39 770 people, an increase in the number of people admitted of 20·5 per cent. The total number of episodes of hospital care increased by 24·0 per cent. Since the population of the Oxford region increased during the study period, it is important to

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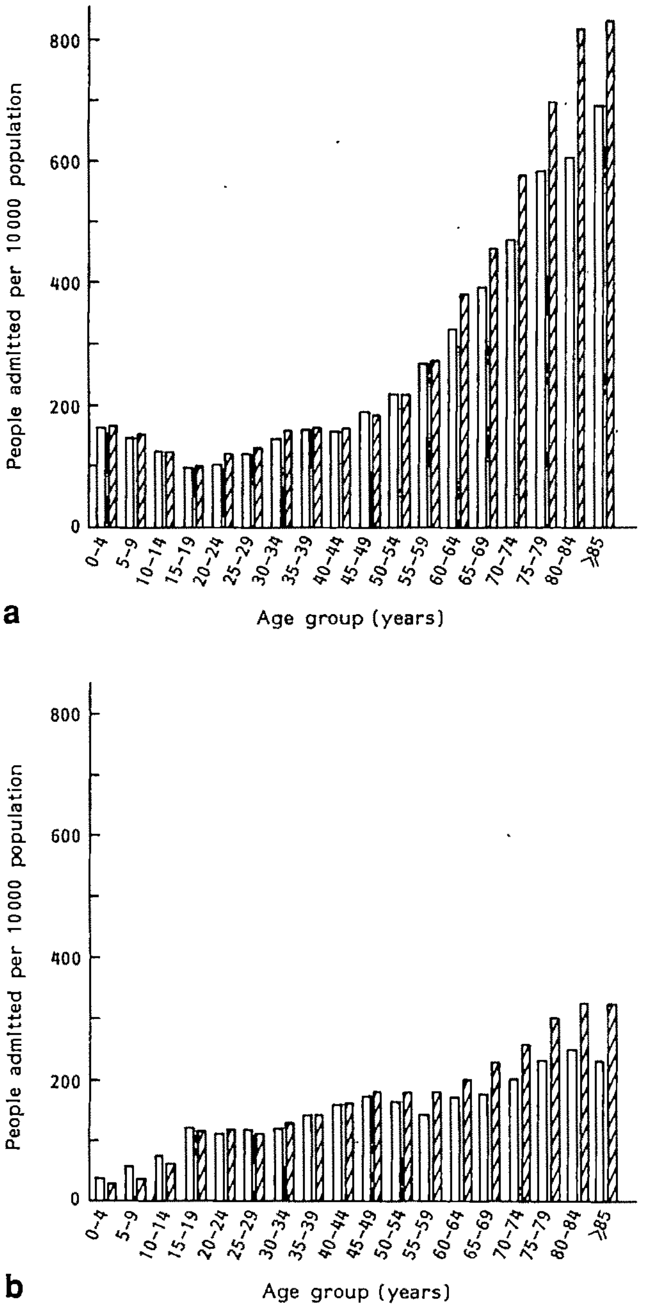

Figure 1 *Age-specific person-based admission rates for general surgery in the Oxford region in 1976* (□) *and 1986* (■) *for* **a** *male and* **b** *female patients*

Table 1 *Number of hospital admissions per 100 people admitted to hospital in 1976 and 1986 according to age and sex*

Age group (years)	M		F	
	1976	1986	1976	1986
0–4	111	113	111	114
5–9	109	109	105	107
10–14	108	108	107	107
15–44	111	112	111	112
45–64	125	129	120	120
65–74	136	141	128	128
≥75	132	143	124	131
Total	120	125	116	118

Values are means

consider treatment rates. Expressed per 10000 resident population, episode-based rates increased from 194 to 224 episodes (15·5 per cent). Person-based rates increased from 164 to 183 individuals admitted (11·6 per cent). Considering inpatients only (i.e. excluding day cases), episode-based rates increased from 169 to 187 (10·7 per cent) and person-based rates from 143 to 154 (7·7 per cent) per 10000 people. When the ratio of total admissions per person admitted was considered, there was a small increase over time. There were no differences in the ratio between the sexes (*Table 1*), but multiple admissions per person increased with age.

Table 2 shows the mean length of stay per inpatient episode and the total time spent in hospital in general surgery per individual per year. A consistent decrease over the years in both the measures was found, and this was consistent in all age groups.

The percentage of patients who underwent emergency admission within 28 days of discharge from hospital care in general surgery showed no clear or consistent change. The risk of such emergency readmission was approximately 3 per 100 people discharged.

Person-based admission rates per 10000 males and females for some conditions for which at least 2000 people were admitted are shown in *Tables 3* and *4*. Some conditions varied substantially from year to year; for example, vasectomy rates rose from 8·1 to 12·3 per 10000 men between 1976 and 1978 and declined to 6·8 per 10000 by 1986. Some showed consistent increases; for example, prostatectomy increased by a mean of 5·3 per cent per annum (*Table 3*). Open prostatectomy for cancer declined by 14·9 per cent per annum, from 0·3 to 0·1 per 10000 males, and open prostatectomy for benign prostatic disease fell by 17·5 per cent, from 4·4 to 0·7 per 10000 men. Transurethral resection of the prostate for cancer increased by 13·0 per cent per annum, from 0·8 to 2·3 per 10000 males, and that for benign prostatic disease increased by 12·7 per cent, from 3·5 to 10·5 per 10000 men. Admission rates for cystoscopy, gastroscopy and sigmoidoscopy all rose significantly.

The rates in *Tables 3* and *4* are all-age rates and therefore reflect the actual workload of surgeons. Age-standardized admission rates for some common surgical conditions (*Table 5*) were calculated to determine the extent to which trends in workload generated by the population were attributable to changes in the age structure. The differences were fairly small; for example, the increase in the prostatectomy rate remained significant and substantial at 4·2 per cent per annum after age standardization and the decline in the appendicectomy rate remained significant at −2·0 and −1·9 per cent per annum for males and females respectively.

There were significant increases in registration rates for cancer of the prostate and colon (significant for men only),

Table 2 *Length of stay in general surgery per episode and per person per year*

Year of admission	Length of stay per episode (days)		Total time in hospital per person (days)	
	M	F	M	F
1976	6·8	7·5	8·2	8·7
1977	6·2	7·1	7·5	8·4
1978	6·0	6·9	7·3	8·0
1979	5·8	6·6	7·0	7·6
1980	5·4	6·1	6·7	7·1
1981	5·3	6·0	6·5	7·1
1982	5·3	6·1	6·6	7·1
1983	5·1	5·7	6·3	6·7
1984	4·8	5·7	5·9	6·6
1985	4·7	5·6	5·9	6·6
1986	4·5	5·3	5·5	6·2

Values are means

Table 3 *Admission rates per 10 000 male population in the Oxford Record Linkage Study area by clinical condition in 1976 and 1986, and percentage annual change between 1976 and 1986*

Clinical condition	OPCS operation code or ICD code*	Total no of patients	Admission rate 1976	Admission rate 1986	Annual change (%)
Prostatectomy	630-5	14 296	8·9	13·6	5·3 (3·5 to 7·2)†
Appendicectomy	441-4	13 293	13·0	10·9	−2·4 (−3·2 to −1·6)†
Vasectomy	651	10 550	8·1	6·8	−2·0 (−5·3 to 1·4)
Abdominal symptoms (no operation)	789*	9 277	6·3	9·7	4·7 (3·3 to 6·2)†
Varicose veins	893-4	5 324	5·3	3·2	2·9 (−0·6 to 6·5)
Incision of anal lesion	480-4	5 266	3·6	5·6	3·5 (1·9 to 5·2)†
Cholecystectomy	522	4 296	3·7	3·5	−1·7 (−3·0 to −0·5)†
Operations on urethra	620-9	3 974	2·3	4·2	6·3 (4·8 to 7·8)†
Operations on peptic ulcer	431-4*	4 035	4·2	2·9	−3·4 (−5·9 to −0·9)†
Laparotomy	402	2 739	3·3	1·9	−6·2 (−8·7 to −3·6)†
Operations for peripheral vascular disease	443*	2 719	2·8	2·0	2·8 (1·4 to 4·2)†
Colectomy	460-1	2 516	1·6	2·7	4·2 (2·6 to 5·8)†

Values in parentheses are 95 per cent confidence intervals. OPCS, Office of Population Censuses and Surveys; ICD, International Classification of Diseases. *Codes with an asterisk are from the ICD[12]; those without are from the OPCS[13]. †$P < 0·05$

Table 4 *Admission rates per 10 000 female population in the Oxford Record Linkage Study area by clinical condition in 1976 and 1986, and percentage annual change between 1976 and 1986*

Clinical condition	OPCS operation code or ICD code*	Total no. of patients	Admission rate 1976	Admission rate 1986	Annual change (%)
Operations on breast	380-9	22 491	18·2	19·2	0·2 (−0·4 to 0·9)
Appendicectomy	441-4	13 324	12·9	10·5	−2·1 (−2·8 to −1·3)†
Abdominal symptoms (no operation)	789*	12 001	7·0	13·6	6·2 (4·9 to 7·6)†
Cholecystectomy	522	10 542	9·4	8·5	−2·1 (−3·1 to −1·0)†
Varicose veins	893-4	9 191	5·2	9·4	5·8 (2·9 to 8·7)†
Excision of cysts	912-5	8 366	7·0	8·0	1·3 (0·2 to 2·4)†
Colectomy	460-1	2 980	1·8	2·7	4·3 (2·2 to 6·5)†
Laparotomy	402	2 780	1·7	3·4	−7·7 (−10·0 to −5·2)†
Incision of anal lesion	480-4	2 503	1·6	2·7	6·2 (4·5 to 7·9)†
Operations on haemorrhoids	490-5	2 219	1·5	2·3	3·5 (1·1 to 6·1)†

Values in parentheses are 95 per cent confidence intervals. OPCS, Office of Population Censuses and Surveys; ICD, International Classification of Diseases. *Codes with an asterisk are from the ICD[12]; those without are from the OPCS[13]. †$P < 0·05$

Table 5 *Percentage change per annum from 1976 to 1986 in age-standardized admission rates for selected operations*

	Sex	Annual change (%)
Inguinal hernia repair	M	0·0 (−1·1 to 1·2)
Prostatectomy	M	4·2 (2·4 to 6·0)*
Colectomy	M	3·2 (1·7 to 4·7)*
	F	3·9 (1·8 to 6·4)*
Operations for peripheral vascular disease	M	2·1 (0·7 to 3·6)*
	F	6·1 (4·3 to 7·9)*
Operations on urethra	M	5·6 (4·1 to 7·0)*
Operations on varicose veins	M	2·6 (−0·9 to 6·2)
	F	5·4 (2·5 to 8·3)*
Appendicectomy	M	−2·0 (−2·9 to −1·2)*
	F	−1·9 (−2·8 to −1·1)*
Cholecystectomy	M	−2·1 (−3·4 to −0·8)*
	F	−2·3 (−3·3 to −1·3)*
Operations on peptic ulcer	M	−4·1 (−6·4 to −1·5)*
	F	1·3 (−1·9 to 4·6)

Values in parentheses are 95 per cent confidence intervals. *$P < 0·05$

and non-significant increases in rates for cancer of the rectum, testis, bladder and breast (*Table 6*). Registration rates for stomach cancer declined significantly.

Discussion

The introduction of the recommendations of the National Steering Group on Health Services Information[16] and those described in *The Next Steps*[17] will facilitate collection of data and linkage of records in all English districts. In the past few years, however, the availability of routine statistical data in England has declined. The national Hospital In-patient Enquiry[1] has not been published since 1985 and full data for the Oxford Record Linkage Study are not yet available for the latter part of the 1980s.

A limitation of National Health Service data, such as that outlined in the present paper, is that they exclude patients treated in private hospitals. There has been an increase in the use of private elective surgical care over the years covered by this study[18] and the true population-based increase in admissions to general surgery will have been greater than that reported here.

Table 6 *Annual percentage change in all-age and age-standardized cancer registration rates in the Oxford Record Linkage Study area, 1976–1986, for selected cancers*

Site	ICD code	Sex	Annual change (%) All-age	Annual change (%) Age-standardized
Stomach	151	M	−1·4 (−2·6 to −0·1)*	−2·4 (−3·6 to −1·1)*
		F	−1·9 (−3·4 to −0·5)*	−2·8 (−4·2 to −1·4)*
Colon	153	M	1·8 (0·9 to 2·7)*	0·6 (−0·2 to 1·5)
		F	0·8 (−0·7 to 2·3)	0·1 (−1·4 to 1·6)
Rectum	154	M	0·8 (−1·0 to 2·6)	−0·3 (−2·1 to 1·5)
		F	0·8 (−0·8 to 2·5)	0·2 (−1·4 to 1·8)
Breast	174	F	0·3 (−0·5 to 1·0)	−0·1 (−0·8 to 0·6)
Prostate	185	M	4·3 (2·9 to 5·9)*	2·7 (1·2 to 4·3)*
Testis	186	M	3·8 (−0·9 to 8·6)	3·2 (−1·5 to 8·0)
Bladder	188	M	1·6 (−0·1 to 3·4)	0·6 (−1·1 to 2·3)
		F	1·5 (−0·8 to 3·8)	0·9 (−1·3 to 3·1)

Values are mean (95 per cent confidence interval). ICD, International Classification of Diseases. $^{*}P < 0{\cdot}05$

The strikingly higher admission rates in general surgery for men in middle age and later life are found nationally in statistics on episodes of care[19]. The population-based perspective may not always be readily apparent to the clinician. For example, the differences in numbers of elderly men treated, compared with elderly women, is not nearly as great as the differences in age–sex-specific admission rates. This is because, in the older age groups, the numbers of women in the population are substantially greater than those of men. Most of the rise over time in the hospital admission rate represented an increase in the number of individuals admitted to hospital, and the rise in multiple admissions per person was small. Time spent in hospital has decreased in general surgery. Because there has been an increase in the proportion of elderly people admitted to general surgery, and because lengths of stay are generally longer in the old, the true age-adjusted decline in length of stay would be even greater than that shown in *Table 2*.

Part of the increase in prostatectomy rates no doubt reflects an increase in prostatic cancer, but it also reflects an increase in the number of operations for benign prostatic hypertrophy. The decline in admissions for peptic ulcer (men) and appendicitis (both sexes) probably reflects a decline in the prevalence or severity of the former[20] and the incidence of the latter[21]. More effective drug therapy may also have reduced surgical admissions for peptic ulcer. The increase in admissions for varicose veins may indicate acceptance by the National Health Service that treatment should be made available. With increasingly explicit decisions about contracts for services, varicose vein surgery may take lower priority in the future. Changes in vasectomy rates may reflect a shift from the National Health Service to the private sector.

In so far as comparable data are available from elsewhere, trends in episode-based admission rates in the Oxford region are similar to those in England as a whole. For example, published data from the Hospital In-patient Enquiry for England in 1979–1985 have shown increases for prostatectomy and operations on varicose veins, small increases for colectomy and abdominoperineal resection, declines for gastrectomy, vagotomy, appendicectomy and cholecystectomy, and no appreciable change for operations on breast or inguinal hernia.

Statistical 'snapshots' of workload in general surgery are useful[22,23]. Continuous workload studies in England and international comparative studies would be valuable in understanding changing patterns of work in general surgery and their implications.

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For the veterinary record

Surgical anatomy of the dog

Vagal system involvement in changes in small bowel motility during restraint stress: an experimental study in the dog

In their recent paper (*Br J Surg* 1993; **80**: 479–83) Dr Muelas and colleagues refer to the ligament of Treitz as an anatomical landmark. This is a mistake that I have seen in many human journals; the duodenum of the dog is not a retroperitoneal structure and there is no ligament of Treitz. It is perhaps most likely that the authors are referring to the duodenocolic ligament.

Surgeons who use animals for experimental research should ensure that they are thoroughly familiar with the regional anatomy of the species used. They should consult the numerous texts available to ensure correct anatomical knowledge, both during the course of the experiment and for purposes of publication.

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Authors' reply

The duodenum of the dog has a mesentery and is not retroperitoneal, which means that the ligament of Treitz does not exist. The recording elements in our study were placed in the duodenum, duodenojejunal junction and proximal jejunum, spaced 30 cm apart. The paper was aimed at doctors and surgeons, who know the ligament of Treitz; this is why we used the term, albeit incorrectly.

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Editor's comment

Authors are asked to ensure that anatomical details are correct for each species. They may wish to highlight similarities or differences between human and animal anatomy.

J. R. Farndon

Editor

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, August, 1078

A selection from the June issue of the American journal.

Inhibition of tumor cell adhesion to lymph nodes by laminin-related peptide and neuraminidase

Sohel M. Islam, MD, Giles F. Whalen, MD, *and* **Setareh F. Sharif, PhD,** *New York, N.Y.*

Background. *Adhesion to lymph nodes, rather than growth stimulation, accounted for preferential colonization of lymph nodes by a metastatic B16 melanoma. We investigated these adhesive interactions.*
Methods. *Four classes of molecules were tested for inhibition of melanoma adhesion to cryostat sections of lymph node.*
Results. *Calcium chelators ethylenediaminetetraacetic acid and ethyleneglycol-bis-(β-aminoethylether)-N, N, N′, N′-tetraacetic acid completely inhibited adhesion (50% adhesion, half-maximal inhibition, at 1 to 3 mmol/L). Cytochalasin B, which impairs contractile microfilaments, inhibited adhesion (60% adhesion at .001 mmol/L, 28% at .01 mmol/L). Colchicine, which disaggregates microtubules, had a similar effect (20% at .01 mmol/L, lowest dose tested). Trypsin slightly increased adhesion (125% adhesion at 10 μg/ml). Neuraminidase, which removed sialic acid residues, inhibited it (50% adhesion at 5 μg/ml). Gly-arg-gly-asp-ser, a peptide with a cell binding sequence of fibronectin, did not consistently inhibit adhesion (69% adhesion at 0.1 mg/ml, 83% adhesion at 1 mg/ml) or substantially differ from gly-arg-gly-glu-ser-pro (59% adhesion at 0.1 mg/ml, 90% adhesion at 1 mg/ml). In contrast, a peptide with a cell binding region of laminin (tyr-ile-gly-ser-arg) inhibited adhesion (50% adhesion at .05 mg/ml).*
Conclusions. *Tumor cell–lymph node adhesion is a calcium-dependent process, requiring a functional cytoskeleton, that is mediated by both sialic acid moieties and trypsin-resistant, laminin-related, adhesion molecules. (SURGERY 1993;113: 676–82.)*

Trauma is a recurrent disease

Galen V. Poole, MD, John A. Griswold, MD,
V. Katherine Thaggard, RN, *and*
Robert S. Rhodes, MD, *Jackson, Miss.*

Background. *Many victims of trauma have a history of repetitive accidental or violent injuries, which implies that trauma is not necessarily a random event. Recurrent trauma is thought to be a problem of urban areas, associated with criminal activities, but there are few data from rural areas that include the victims of nonintentional injuries.*
Methods. *The prior trauma experience of 200 consecutive patients admitted for trauma was compared with that of 100 consecutive emergency nontrauma surgical admissions and 100 elective surgical admissions to a university hospital and level I trauma center.*
Results. *Trauma patients were younger than emergency patients and elective surgery patients. They were more likely to be male than either emergency or elective surgery patients and, along with emergency nontrauma patients, were more likely to be from a racial minority than were elective admissions. Trauma patients were more likely to have had a previous hospitalization for an injury than either emergency patients or elective surgery patients, and a greater proportion of their prior trauma admissions had been within the past 5 years than in the other two groups. There was no difference in the probability of a prior trauma admission between patients admitted with an intentional injury or an accidental injury, but patients whose current admission was for an intentional injury were three times more likely to have had a prior hospitalization as a result of an intentional injury than were patients admitted because of an accidental injury.*
Conclusions. *Trauma is a disease with a high risk of recurrence. This may be related to chronic high-risk behaviors such as alcohol or drug abuse, preexisting psychopathology, and cultural acceptance of violent resolution of personal conflicts, all of which adversely affect patients' lives. The role of intensive preventive measures after an initial injury, and directed toward specific high-risk behavior, should be evaluated. (SURGERY 1993;113:608–11.)*

Blood transfusions and postoperative wound infection

Clyde D. Ford, MD, Gail VanMoorleghem, CTR, *and*
Ronald L. Menlove, PhD, *Salt Lake City, Utah*

Background. *Several studies have suggested an association between blood transfusions and infection in surgical patients. However, previous reports have not documented the relationship of transfusion to specific infection sites and have not adequately explored the importance of timing and type of blood product.*
Methods. *We reviewed the records of all patients undergoing operation for colon cancer at a large community hospital during the years 1974 to 1987. Data on hospital wound and other infections, wound infection risk factors, and type and timing of transfusions were analyzed.*
Results. *Increased wound infection rates were associated with administration of both whole blood and packed red blood cells. However, multivariate analysis suggested that only the administration of packed red cells after operation independently predicted wound infections. Other independent variables were the presence of a colostomy and/or drain. A highly predictive model for wound infection was constructed with these three variables.*
Conclusions. *Blood transfusions, especially with packed red cells, after operation are an independent risk factor for wound infection. (SURGERY 1993;113:603–7.)*

Correspondence

Surgical evaluation at the crossroads

Sir
Mr Pollock's Review in this issue (*Br J Surg* 1993; **80**: 964–6) makes two main points with which few people would disagree, namely that there are substantial practical and ethical problems associated with conducting randomized studies in surgery, and that much valuable information can be derived from well designed and carefully executed non-randomized studies.

However, I believe that it is also useful to consider what one would lose by abandoning randomized surgical trials. The fundamental objection to non-randomized studies is that they are subject to unknown and uncontrolled biases. This is not too worrying if one is looking for substantial differences, but it is devastating if one is looking for subtle differences. Thus the issue comes down to how large a treatment effect is clinically important. As trialists in cardiovascular medicine are quick to point out, modest improvements in the treatment of common conditions (e.g. a 15 per cent relative improvement in survival in trials of secondary prevention following myocardial infarction) can mean many thousands of deaths avoided or delayed. No non-randomized study could ever provide convincing evidence of benefits of this magnitude, because biases of a similar order are almost inevitable in such studies.

Thus, while I accept that one is in the minefield of balancing individual *versus* collective ethics, I would ask whether it is ethical to deny to future patients the possibility of surgery advancing in modest but very relevant steps, rather than awaiting breakthroughs where the benefit shines through even rather poorly controlled studies.

G. D. Murray

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Use of an accident and emergency department observation ward in the management of head injury

Sir
We read with interest the paper by Dr MacLaren and colleagues describing the use of an accident and emergency department observation ward in the management of head injury (*Br J Surg* 1993; **80**: 215–17). The fact that nearly half of the patients, despite meeting published admission criteria, were inappropriately discharged home – particularly when the observation ward was closed at weekends – must be a cause of serious concern. However, we question the suitability of the criteria used for admission for observation ward care following head injury. Persistent confusion or depression of the level of consciousness, skull fracture and an uncertain diagnosis (for instance owing to alcohol, in the young or epilepsy) are surely considered indications for computed tomography (CT) in general hospitals, and progressive focal neurological deficits are an indication for direct referral to a neurosurgical unit without preliminary CT[1].

We also challenge the statement that 'patients with minor head injury are ideally managed on an observation ward . . .'. We accept that the management of the patient with minor head injury, with a history of loss of consciousness or post-traumatic amnesia, Glasgow Coma Score (GCS) 13–15 and no focal neurological deficit is controversial and that there is a need to balance unnecessary admission and diagnostic radiology against the risk of missing an intracranial haematoma. However, admission to a busy accident and emergency observation ward does not guarantee frequent accurate neurological examination[2,3]. In addition, it is impossible to predict accurately from the history, physical examination or GCS which patients will go on to have abnormal findings on CT[2]. Among this group of so-called 'minor head injury' patients, approximately 18 per cent will have abnormal CT scans and 4 per cent will need operation for intracranial lesions[4,5]. While 4 in 100 may appear to be a relatively low risk, the potentially catastrophic personal and economic consequences of missed intracranial haematoma must be borne in mind. Certainly, there is strong evidence that it is the management of these low-risk patients that accounts for much of the excess mortality seen when comparing outcome between hospitals caring for head-injured patients[6].

We therefore believe that CT of the patient with minor head injury should become the proper standard of care both medically and from a resource allocation standpoint. If neurological examination and CT are both normal and there are no other indications for admission, the patient may safely be discharged home[3,4], even in the absence of a responsible observer. This policy would allow up to 80 per cent of all patients with minor head injury to be discharged home[2], producing cost savings from reduction in unnecessary admissions and preserving beds for other patients[2,3].

Finally, we find it clinically and economically illogical for an administration to close an essential part of the accident and emergency department at a time (i.e. weekends) when inpatient and other hospital infrastructure is at its least; this contention is supported by the results of the study.

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Authors' reply

Sir
Dr Brown and colleagues question the criteria for admission after recent head injury in our paper. These criteria were not suggested by the authors but are the published recommendations of a working party set up to investigate the management of head injury in this country[1]. Furthermore, these guidelines clearly state that persistent confusion or depression in the level of consciousness, depressed skull fracture, skull fracture in combination with other signs and focal neurological signs are indications for referral to a neurosurgical unit, and the authors do not suggest otherwise.

Certainly, it would be ideal for every accident and emergency department to have 24-h access to computed tomography for minor head injuries, but most would agree that, since this is clearly not the case at present, researched guidelines on the selection of high-risk patients for observation will benefit both clinician and patient (assuming that adequate beds are made available to meet the predicted number of admissions). Fortunately, the observation ward studied has now been made available for 7 days a week.

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1. Royal College of Surgeons Working Party – Commission on the Provision of Surgical Services. *Report of the Working Party on Head Injuries.* London: RCSE, 1986.

Gastric cancer and *Helicobacter pylori* infection

Sir

We read with interest the article by Dr Buruk and colleagues (*Br J Surg* 1993; **80**: 378–9). An increased rate of gastric malignancy has been observed in developing countries during the past five decades, parallel to a decrease in Western Europe and North America[1,2]. Furthermore, two recent epidemiological studies, the first carried out in Colombia to assess the different serum antibody prevalence in populations with contrasting cancer risks[3], the second performed in China to assess any geographical association between *Helicobacter pylori* antibody prevalence and gastric cancer deaths[4], confirmed a positive relationship between *H. pylori* infection and the development of gastric carcinoma.

However, Buruk and colleagues go further, suggesting that *H. pylori* infection is more frequent in intestinal-type malignancy. They report infection in 88 per cent of subjects with intestinal-type gastric adenocarcinoma, compared with 55 per cent of those with diffuse-type cancer. Unfortunately, they give no data on the age of the patients. Intestinal-type gastric cancer is the most usual form of gastric malignancy in the elderly[5] and *H. pylori* infection also increases with age[6–8]. Thus suggestion of an association between *H. pylori* infection and the histological type of gastric cancer seems imprudent if no adjustment for age is made.

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Laparoscopic abdominoperineal resection of the rectum

Sir

I read with interest the recent Surgical Workshop by Dr Sackier and colleagues describing their technique for laparoscopic abdominoperineal resection of the rectum (*Br J Surg* 1992; **79**: 1207–8). Although I use a similar method and support Dr Sackier's approach, I feel the technique described may not be appropriate for carcinoma as the inferior mesenteric pedicle should be ligated at an earlier stage in the operation.

My technique differs in four important aspects:

1. I use only four cannulas (two right iliac fossa, one supraumbilical, one left iliac fossa); the last is later used for construction of the colostomy.
2. I use a plastic rod 2 cm in diameter and 60 cm long (plastic cover of an Argyle chest drain) inserted rectally to manipulate the rectum and sigmoid colon into the desired position; in my experience this is a useful way of achieving retraction of the rectum.
3. Soon after mobilization of the left colon the inferior mesenteric pedicle is isolated, cleared of fat, clipped and divided distal to the origin of left colic branch.
4. After the perineal dissection, the rectum is pulled down from the perineal wound and resected externally. A purse-string is applied to the proximal end, which is grasped by a forceps via the left iliac fossa cannula, and the colon is exteriorized to form the end colostomy.

I have performed three laparoscopic abdominoperineal excisions of the rectum, two for rectal adenocarcinoma and one for carcinoma of the anal canal. The time taken for the first operation was 4 h and thereafter 2 h 30 min. The patients were discharged at 6, 5 and 6 days; all three are well and free from complications at 6 months.

I believe the above modifications simplify the operation and provide easier mobilization of the colon and rectum. A better cancer operation is performed with effective nodal clearance and, furthermore, only four cannulas are used.

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Laparoscopic truncal vagotomy without drainage

Letter 1

Sir

It is with increasing unease that we read descriptions of vagotomy performed laparoscopically, and the latest paper, by Messrs McDermott and Murphy (*Br J Surg* 1993; **80**: 236), illustrates the cause for our concern. Although there is undoubtedly much dogma in surgery, most modern practice is based on tirelessly performed surgical experiments that often took many years to reach their conclusion. Dragstedt and Owens[1] performed the first truncal vagotomy without drainage for duodenal ulcer 50 years ago. It took 7 years of clinical experimentation before this practice was finally abandoned and a drainage procedure advocated in all cases because of unacceptable side-effects related to gastric stasis in an appreciable proportion of patients[2]. There is no obvious reason why laparoscopic division of the vagal trunks should produce a different clinical outcome to the open procedure, so how many patients have to go through the 'experiment' before we reach the same conclusion as Dragstedt?

It is disappointing to see surgeons repeating the fundamental error of altering the indications for an operation simply because it can be performed laparoscopically. We vigorously dispute the statement that 'The introduction of H_2-receptor antagonists in the management of chronic duodenal ulcer may have resulted in too few patients being submitted to surgery'. The authors would do well to reflect on the fact that it was not the mortality or immediate postoperative problems that led to the abandonment of truncal vagotomy, but the unacceptable incidence of long-term side-effects such as dumping, bile vomiting and postvagotomy diarrhoea.

The scope of laparoscopic surgery is expanding rapidly, but we urge that procedures are not 'rediscovered' simply because they can be performed endoscopically. Lessons learned in the past must not be ignored or we will produce a further generation of patients with ulcers burdened with unpleasant postoperative sequelae.

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1. Dragstedt LR, Owens FM. Supra-diaphragmatic section of the vagus nerves in the treatment of duodenal ulcer. *Proc Soc Exp Biol Med* 1943; **53**: 152–4.
2. Dragstedt LR, Woodward ER. Appraisal of vagotomy for peptic ulcer after seven years. *JAMA* 1951; **145**: 460–5.

Letter 2

Sir

On reading the description of laparoscopic truncal vagotomy without drainage by Messrs McDermott and Murphy (*Br J Surg* 1993; **80**: 236), we found ourselves concerned that enthusiasm for a technique is replacing serious scientific evaluation. The authors' description of the technique and clinical outcome is based on a series of only four patients, which hardly makes it authoritative. In the absence of objective tests of completeness of vagotomy and the results of postoperative endoscopic examination, we believe it is premature to introduce this operation.

Surgical treatment for chronic duodenal ulcer has been in decline for many years. This decline has been hastened by our understanding of the major aetiological role of *Helicobacter pylori* in duodenal ulceration[1]; its eradication by antibiotics with or without bismuth greatly reduces the risk of recurrence[1,2]. Nowadays, with effective acid-suppressing medical treatment as well as our understanding of the role of *H. pylori*, we believe that vagotomy – by whatever surgical means – has a limited place in ulcer management, and we do not think that this technique will tip the balance towards early operation. Truncal vagotomy is not without adverse effects, so a critical evaluation of this technique is required; we suggest that it should be performed only as part of a carefully planned clinical study.

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1. Graham DY. Treatment of peptic ulcers caused by *H. pylori*. *N Engl J Med* 1993; **328**: 349–50.
2. Hentschel E, Brandstatter G, Dragosics B *et al*. The effects of ranitidine and amoxicillin plus metronidazole on eradication of *Helicobacter pylori* and the recurrence of duodenal ulcer. *N Engl J Med* 1993; **328**: 308–12.

Authors' reply

Sir

We thank Messrs Stock, Raimes and Griffin for their interest. We would like to point out that our paper described the technique of laparoscopic truncal vagotomy and did not labour the well rehearsed argument of truncal *versus* highly selective vagotomy. We did refer to a previous paper concerning the rationale of laparoscopic truncal vagotomy[1]. In brief, most patients who undergo truncal vagotomy do not require a drainage procedure, even in Dragstedt's original series, and it should be borne in mind that the percentage of patients presenting to operation for chronic duodenal ulcer with cicatricial pyloric obstruction in the 1940s was higher than in the 1990s. It is our intention to manage symptomatic gastric outlet obstruction, should it arise, by balloon dilatation[2]. The justification for truncal vagotomy and pyloric dilatation has nothing to do with laparoscopic techniques, as the same procedure has been performed at open operation[3,4]. We agree that the long-term complications of ulcer surgery are important, but at least some of these are due to the drainage procedure rather than the vagotomy. Although we agree that there is too much dogma in surgery, we should be no more captive of the dogma of 43 years ago than that of 50 years in the past[5,6].

In response to Messrs Gajraj and Colin-Jones, we did not claim that our series was authoritative. We merely described a technique that has already been performed at open operation and been shown to give good results[3,4]. The adequacy of vagotomy is even more assured using laparoscopic techniques. Our series is continuing but, as their correspondence states, there has been a decline in the role of operation in the management of chronic duodenal ulcer; thus achieving adequate numbers is difficult. The role of *Helicobacter pylori* in the pathogenesis of duodenal ulcer is still unfolding. It is perhaps unreasonable to cite two papers published after our own to advance their argument[7,8]. We might be expected to have due respect for the dogma of the past but we can hardly be expected to foretell the future.

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Prospective randomized comparison of *in situ* and reversed infrapopliteal vein grafts

Sir

In a recent article of considerable interest, Mr Harris and colleagues (*Br J Surg* 1993; **80**: 173–6) presented the results of a randomized comparison of 82 *in situ* and 80 reversed vein grafts for long bypass to the infrapopliteal arteries. For veins $>3{\cdot}5$ mm in diameter, the techniques were equally effective. For veins $\leqslant 3{\cdot}5$ mm in diameter, the authors concluded that a secondary patency rate of 74 per cent for *in situ* grafts and 60 per cent for reversed grafts were not statistically different. However, a difference of 14 per cent is clinically important. In fact, an actuarial relative risk can be calculated as the ratio of cumulative failure rates, yielding a relative risk of 1·54 at 24 months. The risk reduction can be calculated at 0·35; this is also high. Small sample size and not the absence of a true difference is the explanation for the non-significant *P* value. Therefore, the interim data analyses provided by Mr Harris support rather than negate the argument in favour of using the *in situ* technique for long bypass with smaller veins. Finally, there is nothing in the Results to support prosthetic alternatives in this situation.

M. Albers

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Statistical comment

Sir

Dr Albers' letter raises two important statistical issues. The first relates to the idea of a clinically significant difference. If one accepts that a difference of 14 per cent (74 *versus* 60 per cent) between secondary patency rates is clinically important, then it is important to observe that, to have good statistical power (90 per cent), to detect such a difference at the 5 per cent level one would require a study with a sample size of over 400 patients. This is well over twice the total sample size of the study under discussion ($n = 162$), and so the authors' negative results do not exclude the possibility of there being a clinically relevant difference between the two techniques.

The second issue is the subgroup analysis. This is a highly controversial manoeuvre that should only ever be used to *generate* hypotheses[1]. Given the limited size of the overall study, which arguably was too small to detect clinically important differences in the entire population, it is almost pointless to look for modest but clinically important differences in subgroups. I therefore disagree strongly with Dr Albers' assertion that the subgroup results support the *in situ* technique. Both the small sample size for the subgroup analyses and, importantly, the limitations of subgroup analyses *per se*, mean that the data neither support nor refute the use of *in situ* bypass. The data are simply uninformative and, had the authors followed the statistical guidelines of the Journal and presented results accompanied by 95 per cent confidence intervals, this would have been readily apparent.

G. D. Murray

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1. Murray GD. Statistical aspects of research methodology. *Br J Surg* 1991; **78**: 777–83.

Autotransfusion in aortic surgery: the Haemocell 350 cell saver

Sir

We are enthusiastic proponents of autotransfusion during vascular surgery but, while not wishing to hamper any advance in this field, have some reservations about the Haemocell System 350 as described by Mr Kalra and colleagues (*Br J Surg* 1993; **80**: 32–5).

We have both had the opportunity to use this system and agree that it is simple to operate and that the processor copes well with moderate blood loss. However, three patients developed severe coagulopathy after heparin overdosage following autotransfusion using this system, and this complication may have contributed to one death.

In their discussion, the authors claim that heparin was effectively removed during filtration and that the levels in the systemic blood were extremely low when measured at 4 h after operation. In the results, they state that the mean heparin concentration of blood in the collection reservoir before filtration was 5·76 units/ml and 4·93 units/ml in blood returned to the patient. This is a very small drop in concentration and confirms our findings that heparin is not effectively removed during filtration by this system. Considering the short half-life of heparin, it is not surprising that the systemic levels at 4 h were extremely low. Knowledge of the systemic heparin levels immediately before and after reinfusion of the salvaged blood would have been more useful.

The transfusion of a single unit of salvaged blood, containing 2500 units heparin according to the authors' figures, during operation may be perfectly safe, especially if protamine reversal is used and haemostasis is ensured at the end of the procedure. However, if larger volumes of salvaged blood are reinfused, especially if such a transfusion continues after the end of the operation, then appreciable heparin overdosage could occur, especially as filtration efficiency is also impaired by larger volumes of processed blood. Indeed, the manufacturer recommends that the filter is changed after processing 2000 ml blood, although no mention is made of this fact.

There is one final point, which is aimed as much at the reviewers of the manuscript as at the authors themselves, and that is the use of inappropriate statistics. Means and standard errors are used throughout, whereas with such small numbers the appropriate descriptors would be the median and range, especially as most of the parameters measured are almost certainly not distributed normally. Similarly, the illustrations should have been presented as scattergrams, as recommended by the statistical guidelines in the Journal. Statistical analysis should have been performed with an appropriate non-parametric tool, such as the Wilcoxon signed rank test, rather than Student's paired *t* test.

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M. Horrocks*

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Authors' reply

Sir

I am grateful to Mr Beard and Professor Horrocks for their interest and comments. We took advice on the statistics from Dr Brian Farragher, who is the Head of Medical Statistics at our hospital. The distributions of the data were checked and found to be normal, except for bilirubin, which was marginally different. We chose line graphs rather than scattergrams because this is the format adopted in previous articles on this subject and made comparison easier.

The removal of plasma constituents was calculated in the following way:

$$\text{Plasma volume (ml)} = \frac{\text{blood volume (ml)} \times (100 - \text{haematocrit})}{100}$$

then

$$\text{Total quantity of constituent} = \frac{\text{plasma volume} \times \text{measured quantity of constituent}}{\text{unit volume of plasma constituent}}$$

and

$$\text{Percentage removal} = \frac{\text{total collection quantity} - \text{total reinfusion quantity (ml)}}{\text{total collection quantity (ml)}} \times 100$$

The plasma volume (collection) was 283 ml of heparin 576 units/ml, giving a concentration in the collection bottle of 1630 and for the reinfusion 913. Percentage removal was 44.

We did not see any case of coagulopathy in this series, but reinfusion volumes were small. We are aware that the operation of aortobifemoral bypass is commonly associated with a decrease in fibrinogen levels, a situation that can be compounded by heparin. Like Beard and Horrocks, we worry about the quantity of heparin that may be administered, particularly in patients who have ruptured aneurysm.

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Statistical comment

Sir

Mr Beard and Professor Horrocks are correct to point out that the statistical presentation and analysis of the data could have been improved. The methods used may or may not be appropriate, but unfortunately the authors do not present sufficient data to allow the reader to judge. In the absence of such supporting data, a non-parametric approach would have been preferable to the normal-based analysis adopted.

It would have been invaluable to have had the individual patient data plotted. This is particularly the case in a study where safety rather than efficacy is an important issue: one is not so interested in the average change of certain parameters but rather in seeing how frequently patients had seriously deranged values.

G. D. Murray

Statistical Consultant
BJS

Heparinized saline to aid aspiration of blood clots during laparoscopy

Sir

Peroperative bleeding with clot formation during laparoscopic surgery resorbs light and reduces the quality of video imaging. In addition, the removal of intraperitoneal blood may be an important contributor to total operating time. Meticulous dissection and haemostasis are therefore golden rules of endoscopic surgery.

The aspiration of intraperitoneal blood is often difficult and time consuming owing to blockage of the suction cannula or the presence of large clots. High-pressure irrigation devices may clear the operative field and aid clot fragmentation, but they have the disadvantage of introducing potentially large volumes of fluid into the abdominal cavity. This fluid eventually has to be aspirated (with concomitant loss of the pneumoperitoneum), further adding to the operating time. These devices are also expensive, bulky and ineffective at breaking up smaller clots.

We have therefore adopted a policy of irrigating the operative field with 100 ml heparinized saline 7500 units/l before endoscopic dissection has begun. This prevents coagulation of any intraperitoneal blood and greatly facilitates its aspiration. Over 100 laparoscopic procedures frequently requiring irrigation, such as cholecystectomy, appendicectomy and colectomy, have been performed using this technique. We have experienced a marked reduction in the time spent fragmenting large clots, unblocking the suction cannula and clearing the peritoneal cavity of fluid. We recommend the use of heparinized saline to prevent coagulation of intraperitoneal blood during laparoscopic procedures.

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Clinical trial of tamoxifen in patients with irresectable pancreatic carcinoma

Sir

The paper by Mr Taylor and colleagues (*Br J Surg* 1993; **80**: 384–6) not only does not show a survival advantage with tamoxifen treatment but, considering the size of the trial (which is relatively small), there is a disturbing trend to reduced survival in treated patients. This is entirely analogous to our published experience with gastric carcinoma[1]. We also went on to show that oestrogen receptor-positive cell lines are in fact directly stimulated by both tamoxifen and oestrogen[2]. While this is a resoundingly negative result, it surely does question whether an alternative hormonal approach to these gastrointestinal cancers could be made, for example, by reducing concentrations of oestrogen rather than using antagonists that clearly have agonist action.

D. L. Morris

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1. Harrison JD, Morris DL, Ellis IO, Jones JA, Jackson I. The effect of tamoxifen and estrogen receptor status on survival in gastric carcinoma. *Cancer* 1989; **64**: 1007–10.
2. Harrison JD, Watson S, Morris DL. The effect of sex hormones and tamoxifen on the growth of human gastric and colorectal cancer cell lines. *Cancer* 1989; **63**: 2148–51.

Symptomatic outcome after laparoscopic cholecystectomy

Sir

The outcome after laparoscopic cholecystectomy reported by Messrs Wilson and Macintyre (*Br J Surg* 1993; **80**: 439–41) is similar to that found in our own review of 90 consecutive patients treated by this means who were also consulted by postal survey to assess the results of treatment. We found that for 75 per cent of patients symptoms were completely relieved by operation, 14 per cent were improved, 11 per cent were symptomatically unchanged and none was worse.

We were particularly interested to see comparison made with herniorrhaphy (as well as with open cholecystectomy); this comparison showed a similar incidence of abdominal pain, nausea, flatulence, food intolerance and heartburn – symptoms usually suggestive of gallstones. We believe that it is important, when assessing the results of operation, to remember that the normal population experiences symptoms from time to time and that this does not necessarily indicate disease; similarly, the occasional experience of similar symptoms after operation need not indicate failure of treatment.

One aspect of outcome that Wilson and Macintyre did not address was the surgical wound. Wound pain appears to be the major factor in delaying full postoperative recovery and return to normal activities. Laparoscopic cholecystectomy has the clear advantage that wound-related problems are much less common and less severe than after open cholecystectomy. This fact was reflected in our series, in which the median time before patients felt able to return to normal activities or to work was less than a fortnight.

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R. H. K. Gompertz
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Ultrasonography in the diagnosis of gallbladder polyps

Sir

We read with interest the article by Dr Özdemir and colleagues (*Br J Surg* 1993; **80**: 345), in which it was concluded that ultrasonographic criteria for the diagnosis of gallbladder polyps need to be better established to improve the diagnostic reliability of the method. This condition very much contrasts with those of a number of other studies[1–3], including a recent paper on 182 Chinese people with polypoid lesions of the gallbladder[4] which showed a sensitivity of 90 per cent for ultrasonography, 24 per cent for oral cholecystography, 62 per cent for computed tomography and zero for endoscopic retrograde cholangiography. Furthermore, although Özdemir *et al.* detected 13 patients with gallbladder polyps, no mention is made of the nature of these lesions, whether true neoplasms or pseudotumours such as cholesterol polyps, hyperplasia and heterotopia.

L. Basso
A. Tocchi

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Italy

1. Ito T, Takami M, Kosuge T *et al.* Ultrasonographic diagnosis of polypoid lesions of the gallbladder. *Journal of Clinical Surgery* 1986; **41**: 25–30.
2. Hachisuka K, Yamaguchi A, Isoya M, Matsushita M. Choice of surgical treatment for elevated lesions of the gallbladder. *Journal of Clinical Surgery* 1986; **41**: 41–6.
3. Wan YL, Wang WZ, Li T, Tang XY. Polypoid lesions of the gallbladder. *Chung Hua Wai Ko Tsa Chih* 1989; **27**: 450–3.
4. Yang HL, Sun YG, Wang Z. Polypoid lesions of the gallbladder: diagnosis and indications for surgery. *Br J Surg* 1992; **79**: 227–9.

Book reviews

Surgical Audit. 2nd ed.

A. Pollock and M. Evans. 240 × 160 mm. Pp. 278. Not illustrated. 1993. Oxford: Butterworth–Heinemann. £32·50.

As Chair of the surgical audit in the Bristol Royal Infirmary I sometimes muse, while boring morbidity and mortality detail drones on: 'Why should surgeons audit?' This same question is posed in the preface to *Surgical Audit* by Pollock and Evans. The beginnings of the answer are 'Everybody in the world is entitled to the same high quality of medical care. This must not be a pipe dream and the World Health Organization aims at this target by the year 2000'. This is the beginning of the rationale of audit. It clearly *is* a pipe dream and a tragedy that the WHO has such misguided and unobtainable aspirations. Surgeons must not be misguided, however, but within their domain strive for the best for their patients. Audit is one way in which that aim might be achieved.

The second edition of this book is considerably longer than the first and printed on poorer quality paper, but the authors have audited their first edition to produce an excellent second. It continues to be an entertaining and educational work with its introductory aphorisms and remarks, my favourite being: 'I beseech you, in the bowels of Christ, think it possible that you may be mistaken' (ascribed to Oliver Cromwell in 1650).

The book is eminently readable and set out in a pleasingly varied style. Important elements are clearly listed and highlighted. It can be dipped into if you wish to read self-contained sections. The topics progress from the history and definition of audit, through audit of structure and process to the audit of outcome measures. Patients are not forgotten, with consideration given to ethical, experimental and patient satisfaction issues. *The British Journal of Surgery* and its editorial team are audited in detail in a section on 'Audit of publications'. The reader will have to buy the book to see what the authors say about the Journal.

All sections of the book have been comprehensively updated, whether this be to cover new technology, such as laparoscopic procedures, or medicolegal or ethical issues. Some points remain unanswered, such as the effects of cost containment, the search for efficiency, and disease or illness priorities. The front cover has changed from blood red to surgical green. I think this means 'go' (to your bookshop to buy a good enjoyable read). I look forward to a third edition in which the authors will demonstrate that the audit process and the resources poured into it have produced worthwhile results.

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Pediatric Surgery. 2nd ed.

K. W. Ashcraft and T. M. Holder (eds). 286 × 220 mm. Pp. 1062. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US $170.

The paediatric surgeon stands alone as the last true generalist in the increasingly specialized field of general surgery. The discipline is determined by the age of the patient rather than any particular region of the anatomy. Despite this, there is a tendency in the larger centres for specifically trained paediatric urologists to handle all genitourinary surgery in the child. In addition, there has been a gradual but steady erosion of certain conditions to adult-orientated specialists – such as spina bifida to neurosurgeons, burns to plastic surgeons, lung surgery to thoracic surgeons and cystic lesions of the neck to ear, nose and throat surgeons.

Pediatric Surgery, edited by Keith Ashcraft and Tom Holder, is the most readable of the three major texts on the subject emanating from the USA. With 111 contributions from experts in the field (all bar one from the States), the editors have succeeded in producing a textbook that encompasses the interests of most paediatric surgeons. There is a much expanded section on trauma, the leading cause of death in children over 1 year old, with less devoted to areas of peripheral interest.

There are excellent chapters on physiology and nutritional support. Oesophageal conditions are particularly well covered, with extensive and up-to-date references reflecting the editors' expertise in the subject. The sections on congenital anomalies of the gastrointestinal system and genitourinary tract are of a high standard, but I was disappointed by a number of chapters, notably those on ethical considerations, foreign bodies, intussusception, hernia and undescended testis; these unfortunately detract from the overall value of the book. Congenital heart defects are among the most common associated anomalies encountered in paediatric surgical practice (25 per cent in oesophageal atresia) and a chapter dealing with the principles of management of these anomalies would have been extremely valuable. These minor criticisms aside, I would strongly recommend this book to all trainees in paediatric surgery and, if medical libraries were to purchase only one book on the subject, this is the one I would suggest.

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Surgery of the Oesophagus. 2nd ed.

T. P. J. Hennessy and A. Cuschieri (eds). 253 × 192 mm. Pp. 356. Illustrated. 1992. Oxford: Butterworth–Heinemann. £70.

This excellent text deals comprehensively with all aspects of oesophageal surgery. The majority of the book has been written by the two senior authors and, in contrast to its multiauthor rivals, there is virtually no repetition. All the chapters are well written and superbly referenced. The opening chapter on anatomy and physiology of the oesophagus is outstanding, as is the section on oesophageal tumours.

Typographic errors are minimal, although occasionally amusing. I am not sure how many takers there would be for an oesophageal dilatation to 55 mm. Illustrations and radiographs are plentiful and generally of good quality, although the drawing of the cardiac orifice and incisura from inside the stomach looks more like something one would expect to see at the Tate Gallery. There are just a few areas where I would disagree with the authors. For instance, the discussion of medical therapy for stricture secondary to gastro-oesophageal reflux is superficial but this is, after all, a surgical text and it is not often that one can reach three-quarters of the way through such books before arriving at the first area of disagreement.

At 350 pages this book is concise and at £70 cheap in comparison to its competitors. It should be on the desk of every surgeon with an interest in the oesophagus and I would recommend it whole-heartedly to trainees who wish to develop an interest in oesophageal surgery.

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Baillière's Clinical Gastroenterology: International Practice and Research. Vol. 6. No. 4

M. Sackman (ed.). 231 × 154 mm. Pp. 200. Illustrated. 1992. London: Baillière Tindall. £27·50.

Biliary stones are often multifaceted; this is indeed true both of their diagnosis and their management. This is a multiauthor specialist text, aiming to review the state of the art in diagnostic procedures and gallstone disease. The authorship is highly international, predominantly from continental Europe and the USA. Is it the impact and cost of the high-technology approaches to biliary stones that result in there being only a single contribution from the UK?

There is a first-rate general overview of the symptoms of gallstone disease, followed by a series of articles in which the variety of treatment choices – surgery, oral dissolution, lithotripsy, direct solvent dissolution and endoscopic approaches – are surveyed. A notable editorial weakness is repetition. For example, the chapter on diagnostic procedures contains no general introduction, but defines the imaging criteria that may identify stones suitable for different forms of non-surgical treatment; these criteria are then repeated many times over in the ensuing chapters. The chapters on surgery make an interesting contrast. An enthusiastic but thoughtful analysis of 777 laparoscopic cholecystectomies, with results followed through until September 1991, is followed by a philosophical and generalist overview by Malt on the role of surgery for gallstones.

The single wisest paragraph in this book comes from Malt's chapter:

> 'The big problem in deciding how to treat cholelithiasis and its complications is that decisions about what is feasible and appropriate are often made by specialists who do not normally treat patients with gallstones except with a single therapeutic modality at their command'.

Inevitably, clinicians move within the constraints of local talent. This book offers an up-to-date view on what more distant talents have to offer.

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Rob and Smith's Operative Surgery. Genitourinary Surgery. Endoscopic Procedures, and Vols 1 and 2. 5th ed.

H. N. Whitfield (ed.). 283 × 223 mm. Pp. 856. Illustrated. 1993. Oxford: Butterworth–Heinemann. £250.

Hugh Whitfield as editor and a major author, together with the other authors and illustrators, are to be congratulated on this splendid production. The single volume on urology in the 4th edition of 1986 has now been expanded to three slimmer volumes, one devoted to endoscopic procedures. This reflects the remarkable recent innovations in operative technique. Endoscopic surgery, which has been applied to the lower urinary tract for more than 60 years, is now finding application in the ureter, kidney and peritoneal cavity. It is a pity that the lithoclast was just too late to be included. Other important new procedures include the use of sacral anterior root stimulators and a whole range of augmentation and replacement cystoplasties and continent urinary diversion techniques. The management of benign prostatic hyperplasia is another rapidly changing field. In this edition various open prostatectomies, electroresection, cold punch resection, bladder neck incision, hyperthermia, stents and balloon dilatation are all described, but not laser prostatectomy. Which of these will be in the next edition?

This book gives an accurate picture of urology in the early 1990s. The text and illustrations are sufficiently clear to guide the surgeon through each procedure. The cost is equivalent to about 6 h in an intensive care unit. I give it three hearty cheers.

G. J. Fellows

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Atlas of Surgical Operations. 7th ed.

M. J. Houston and P. McCurdy (ed). 360 × 260 mm. Pp. 484. Illustrated. 1993. New York: McGraw–Hill. £76·50.

I must confess that I am not an enthusiastic advocate of surgical atlases, even those to which I have contributed. I believe that surgical technique should be learnt in the operating room, assisting 'the master', discussing the indications for the operation, variations in technique and postoperative management. This book achieves a similar end in a superficial fashion. It is presented such that it will lie open comfortably on a side table in the operating room where its excellent line drawings can act as a surgical 'cook book'. It will thus be valuable for surgeons working in areas far removed from expert help. But should they be encouraged to attempt resection of a Klatskin tumour, liver trisegmentectomy, or carotid endarterectomy?

The introductory chapters consist of a didactic view of the art of surgery but often lack scientific justification. For instance, 'Fine silk … creates a minimum of tissue reaction and prevents secondary haemorrhage when securely knotted' and 'a day or two of intensive therapy with antibiotics may be desirable …', while surprisingly there is no mention of prophylaxis against deep vein thrombosis. The advocacy of gentle tissue handling is rather negated by the extensive use of clamps and Babcock tissue holders on the intestine.

In summary, this is a beautifully illustrated atlas that makes a worthy companion to the extensive library of similar works and will no doubt find its (expensive) way into operating rooms around the world, especially in the USA.

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Notices and announcements

12–16 September 1993
6th World Meeting on Impotence
Singapore
Information: Secretariat 6th WMI, Department of Obstetrics and Gynaecology, National University Hospital, Lower Kent Ridge Road, Singapore 0511

14–17 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

15–17 September 1993
Nottingham European Organization for Research and Treatment of Cancer Joint Breast Cancer Meeting
Nottingham, UK
Information: Mrs Wendy Bartram, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

29 September to 1 October and 2 October 1993
Principles of Colon and Rectal Surgery, and Biofeedback for Pelvic Floor Disorders/Endorectal Ultrasonography
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue South-east, Minneapolis, Minnesota 55414, USA

29 September to 2 October 1993
(dates vary)
Advanced Laparoscopic Surgery Courses
Amsterdam, The Netherlands
Information: Factory/Congress Office, Bloemgracht 169, 1016-KN, Amsterdam, The Netherlands

12–14 October 1993
Noninvasive Vascular Investigation Course
London, UK
Information: Anne Taft, Vascular Unit, St Mary's Hospital Medical School, London W2 1NY, UK

17–23 October 1993
Surgery of the Liver, Biliary System and Pancreas
Edinburgh, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

27 October 1993
Monitoring and Quality Control During Carotid Endarterectomy
Leicester, UK
Information: Mr A. R. Naylor, Department of Surgery, Leicester Royal Infirmary, Leicester LE1 5WW, UK

1–5 November 1993
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

18–19 November 1993
Vascular Surgical Society of Great Britain and Ireland Annual Meeting
Manchester, UK
Information: Mr P. L. Harris, VSS Secretary, Link 8c, The Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

18–20 November 1993
Combined Meeting of the European Conference on General Thoracic Surgery and 2nd Annual Meeting of the German Society for Thoracic Surgery
Heidelberg, Germany
Information Administrative Secretariat, c/o AKM Congress Service GmbH, Obere Schanzstraße 18, D-79576 Weil am Rhein, Germany

30 November to 2 December 1993
Eighth International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr S. C. S. Chung, Combined Endoscopy Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

23–28 January 1994
18th International Congress of Radiology
Singapore
Information: 18th ICR '94, Kent Ridge, PO Box 1052, Singapore 9111

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, 12203 Berlin, Germany

21–23 February 1994
Seventh Annual Congress of the North American Society of Phlebology on the Advances in Medical and Surgical Treatment of Venous Disorders
Wilea, Hawaii, USA
Information: North American Society of Phlebology, 523 Encinitas Boulevard, Suite 108, Encinitas, California 92024, USA

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Cleveland, Ohio 44195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians-Universität Munich, Klinikum Großhadern, Chirurgische Klinik, Marchioninistraße 15, D-8000 Munich 70, Germany

20–22 April 1994
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association of Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua do Ouvidor 60/414, 20040-030 Rio de Janeiro, Brazil

2–7 October 1994
World Congress of Gastroenterology
Los Angeles, California, USA
Information: World Congress of Gastroenterology Secretariat, 655 15th Street, NW, Suite 300, Washington, DC 20005, USA

13–16 November 1994
XXIX World Congress of the International College of Surgeons
London, UK
Information: Jacqueline Webber Associates, 22 Park Farm Road, Kingston upon Thames, Surrey KT2 5TQ, UK

19–22 November 1994
XIXth European Society for Medical Oncology Congress
Lisbon, Portugal
Information: Secretariat, ESMO, Via Soldino 22, 6900 Lugano, Switzerland

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

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Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

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Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

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